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Pharmaceutical Sciences

1980

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Remington's Pharmaceutical Sciences . . . *a treatise on the theory and practice of the pharmaceutical sciences, with essential information about pharmaceutical and medicinal agents; also a guide to the professional responsibilities of the pharmacist as the drug-information specialist of the health team . . . A textbook and reference work for pharmacists, physicians, and other practitioners of the pharmaceutical and medical sciences.*

Over 1000 illustrations and tables

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Chapter 83

Solutions, Emulsions, Suspensions and Extractives

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aqueous solutions
sweet or other viscid aqueous solutions
nonaqueous solutions
emulsions
suspensions
maceration
extraction
extractives

The dosage forms described in this chapter may be prepared by dissolving the active ingredient(s) in an aqueous or nonaqueous solvent, by suspending the drug (if it is insoluble in pharmaceutically or therapeutically acceptable solvents) in an appropriate medium, or by incorporating the medicinal agent into one of the two phases of an oil and water system. Such solutions, suspensions, and emulsions are further defined in subsequent paragraphs but some, with similar properties, are considered elsewhere. The appropriate chapters (see the index) should be consulted for information on the preparation and characteristics of those liquid preparations that are intended for ophthalmic or parenteral use.

Much has been written during the past decade about the biopharmaceutical properties of, in particular, the solid dosage forms. In assessing the bioavailability of drugs in tablets and capsules, many researchers have first studied the absorption of drugs administered in solution.

Since drugs are absorbed in their dissolved state, frequently it is found that the absorption rate of oral dosage forms decreases in the following order: aqueous solution > aqueous suspension > tablets or capsules. The bioavailability of a medicament, for oral ingestion and absorption, should be such that eventually all of the drug is absorbed as it passes through the gastrointestinal tract, regardless of the dosage form. There are a number of reasons for formulating drugs in forms in which the drug is not in the molecular state. These are: (a) improved stability, (b) improved taste, (c) low water solubility, (d) palatability, and (e) ease of administration. It becomes apparent, then, that each dosage form will have advantages and disadvantages.

The pharmacist handles liquid preparations in one of three ways. First, he may dispense the product in its original container. Secondly, he may buy the product in bulk and repackage it at the time a prescription is presented by the patient. Lastly, he may compound the solution, suspension, or emulsion in the dispensary. Compounding may involve nothing more than mixing two marketed products in the manner indicated on the prescription or, in specific instances, may require the incorporation of active ingredients in a logical and pharmaceutically acceptable manner into the aqueous or nonaqueous solvents which will form the bulk of the product.

The pharmacist, in the first instance, depends on the manufacturer to produce a product that is effective, elegant, and stable when stored under reasonably adverse conditions. Most drug manufacturers attempt to guarantee efficacy by evaluating their products in a scientifically acceptable manner but, in some instances, such efficacy is relative. For example, cough mixtures marketed by two different manufacturers may contain active ingredients in the same therapeutic class and it becomes difficult to assess the relative merits of the two products. In such instances the commercial advantage gained by one over the other may be based on product elegance. Thus, color, odor, taste, pourability, and homogeneity are important pharmaceutical properties.

The stability of the active ingredient in the final product is of prime concern to the formulator. In general, drug substances are less stable in aqueous media than in the solid dosage form and it is important, therefore, to properly buffer, stabilize, or preserve, in particular, those solutions, suspensions, and emulsions that contain water. Certain simple chemical reactions can occur in these products. These may involve an ingredient-ingredient interaction (which implies a poor formulation), a container-product interaction (which may alter product pH and thus, for pH-sensitive ingredients, be responsible for the subsequent formation of precipitates) or a direct reaction with water (i.e., hydrolysis). The most complicated reactions usually involve oxygen. Vitamins, essential oils, and almost all fats and oils can be oxidized. Formulators usually use the word *autoxidation* when the ingredient(s) in the product react with oxygen but without drastic external interference. Such reactions must be initiated by heat, light (including ultraviolet radiant energy), peroxides or other labile compounds, or heavy metals such as copper or iron. This initiation step results in the formation of a free radical (R*) which then reacts with oxygen:

$$R^* + O_2 \rightarrow RO_2^* \text{ (peroxy radical)}$$

$$RO_2^* + RH \rightarrow ROOH + R^*$$

The free radical is thus regenerated and reacts with more oxygen. This propagation step is followed by the termination reactions.

$$RO_2^* + RO_2^* \rightarrow \text{inactive product}$$

$$RO_2^* + R^* \rightarrow \text{inactive product}$$

$$R^* + R^* \rightarrow \text{inactive product}$$

The effect of trace metals can be minimized by the use of citric acid or EDTA (i.e., by use of sequestering agents). Antioxidants, on the other hand, may retard or delay oxidation by reacting with the free radicals formed in the product. Examples of antioxidants are the propyl, octyl, and dodecyl esters of gallic acid, butylated hydroxyanisole (BHA), butylated tocopherols or vitamin E. For a more detailed account of the prevention of oxidative deterioration in pharmaceuticals the paper by Ostendorf[1] should be consulted.

The problem of drug stability has been well known to pharmaceutical scientists but, during the past few years, secondary and, in some respects, more serious problems have confronted the manufacturer of liquid preparations. Many pharmaceutically diverse products as baby lotion and milk of magnesia have been recalled from the market because of bacterial contamination. In a survey of retail

liquid antacid preparations containing magnesium hydroxide, it was found that 30.5% of the finished bottles were contaminated with *Pseudomonas aeruginosa*. The aerobic plate count ranged from less than 100 to 9,300,000 organisms/gram. Other examples could be cited but the range of microorganisms which can contaminate the liquid preparation includes the *Salmonella* sp., *E. coli*, certain *Pseudomonas* sp., including *P. aeruginosa*, and *Staphylococcus aureus*. Bruch[2] describes the types of microorganisms found in various products and attempts to evaluate the hazards associated with the use of nonsterile pharmaceuticals.

The USP recommends that certain classes of products be routinely tested for microbial contamination, e.g., natural plant and animal products, for freedom from *Salmonella* species; oral solutions and suspensions, for freedom from *E. coli*; articles applied topically, for freedom from *P. aeruginosa* and *S. aureus*; articles for rectal, urethral or vaginal administration, for total microbial count.

Products may become contaminated for a number of reasons. First, the raw materials used in the manufacture of solutions, suspensions, and emulsions are excellent growth media for bacteria. Water, in particular, must be handled with care but substances such as gums, dispersing agents, surfactants, sugars, and flavors can be the carriers of bacteria which ultimately contaminate the product. A second source of contamination is equipment. Bacteria grow well in the nooks and crevices of pharmaceutical equipment (and in the simple equipment used in the dispensary). Such equipment should be thoroughly cleaned prior to use. Lastly, environment and personnel can contribute to product contamination. Hands and hair are the most important carriers of contaminants. General cleanliness is thus vital. Head coverings must be used by those involved in the manufacturing process and face masks should be used by those individuals suffering from colds, coughs, hay fever, and other allergic manifestations.

The factors cited above relate to good manufacturing practice. However, the formulator can add a preservative to the product and decrease the probability of product contamination. If the product contains water, it is almost mandatory to include a preservative in the formulation. It must be stressed that this in no way replaces good in-plant control but merely provides further assurance that the product will retain its pharmaceutically acceptable characteristics to the patient level.

The major criteria that should be considered in selecting a preservative are: (a) it should be effective against a wide spectrum of microorganisms; (b) it should be stable for the shelf-life of the product; (c) it should be nontoxic; (d) it should be nonsensitizing (e) it should be compatible with the ingredients in the dosage form; (f) it should be relatively free of taste and odor.

Preservatives may be used alone or in combination with each other to prevent the growth of microorganisms. Ethanol is a highly effective preservative. It is used at the 15% level in acidic media and at the 18% level in neutral or slightly alkaline media. Isopropyl alcohol is a fairly effective agent but can be used only in topical preparations. Propylene glycol, a dihydric alcohol, has germicidal activity similar to that of ethanol. It is normally used at the 10% concentration level.

A 0.5% solution of phenol is a good preservative but it is limited in that it has its own characteristic odor, and reacts chemically with many of the drugs and adjuvants which are incorporated in liquid preparations.

The use of hexachlorophene, a germicidal agent which is highly effective against gram-positive organisms, is restricted to those preparations which are intended for external use only. Several years ago, an incorrectly formulated baby powder (which was found to contain 6.5% hexachlorophene) was responsible for the deaths of 30 French infants. Because of this and other evidence, this substance can be used as a preservative only if its concentration in the final product is 0.1% or less. However, certain liquid preparations (e.g., Hexachlorophene Liquid Soap USP) are available. The hexachlorophene content is usually 0.25% in the USP product.

Organic mercury compounds are powerful biostatic agents. Their activity may be reduced in the presence of anionic emulsifying or suspending agents. They are not suitable for oral consumption but are used at the 0.005% concentration level in ophthalmic, nasal, and topical preparations.

Benzoic acid is effective only at pH 4 or less. Its solubility in certain aqueous preparations is poor and, in those instances, sodium benzoate may be utilized. Sorbic acid has a broad range of antimycotic activity but its antibacterial properties are more limited. It is effective only at a pH of less than 5.

Quaternary ammonium surface-active agents, e.g., benzalkonium chloride, exhibit an objectionable off-taste and have been reported to be incompatible with a number of anionic substances. In concentrations of 1:5000 to 1:20,000 they are used in ophthalmic preparations.

3-Phenylpropan-1-ol (hydrocinnamyl alcohol) is claimed to be more effective than 2-phenylethanol and benzyl alcohol in inhibiting the growth of *P. aeruginosa*, and it has been suggested that this substance may be a suitable preservative for oral suspensions and mixtures.

The methyl and propyl esters of para-hydroxybenzoic acid (the parabens) are widely used in the pharmaceutical industry. They are effective over a wide pH range (from about 3 to 9) and are used at up to about the 0.2% concentration level. The two esters are often used in combination in the same preparation. This achieves a higher total concentration and the mixture is active against a wide range of organisms. The hydroxybenzoates are effective against most organisms; however, their activity may be reduced in the presence of nonionic surface-active agents because of binding.

It should now be obvious that when the pharmacist dispenses or compounds the various liquid preparations he assumes responsibility, with the manufacturer, for the maintenance of product stability. The USP includes a section on stability considerations in dispensing practice. This section of the compendium should be studied in detail.

Certain points are self-evident. Stock should be rotated and replaced if expiration dates on the label so indicate. Products should be stored in the manner indicated in the compendium; e.g., in a cool place, a tight, light-resistant container, etc. Further, products should be checked for evidence of instability. With respect to solutions, elixirs, and syrups, precipitation and evidence of microbial or chemical gas formation are the two major signs of instability. Emulsions may cream but if they break (i.e., there is a separation of an oil phase) the product is considered to be unstable. Caking is a primary indication of instability in suspensions. The presence of large particles may mean that excessive crystal growth has occurred.

The USP states that repackaging is inadvisable. However, if the product must be repackaged, care and the container specified by the compendium must be used. For example, a plastic container should never be used if a light-resistant container is specified by the compendium. If a product is diluted, or where two products are mixed, the pharmacist should utilize his knowledge to guard against incompatibility and instability. Oral antibiotic preparations constituted into liquid form should never be mixed with other products. Since the chemical stability of extemporaneously prepared liquid preparations is often an unknown, their use should be minimized and every care taken to insure that product characteristics will not change during the time it must be used by the patient.

Aqueous Solutions

A solution is a homogeneous mixture that is prepared by dissolving a solid, liquid, or gas in another liquid and represents a group of preparations in which the molecules of the solute or dissolved substance are dispersed among those of the solvent. Solutions may also be classified on the basis of physical or chemical properties, method of preparation, use, physical state, number of ingredients, and particle size. The narrower definition herein limits the solvent to water and excludes those preparations that are sweet and/or viscid in character. This section includes, therefore, those pharmaceutical forms that are designated as *Waters, Aqueous Acids, Solutions, Douches, Enemas, Gargles, Washes,* and *Juices.*

This section, and the chapter as a whole, must be considered as part of a broad subject that is based on principles presented in several chapters of Part 2.

Water

The major ingredient in most of the dosage forms described herein is water. Water is used both as a vehicle and as a solvent for the desired flavoring or medicinal ingredients. Its tastelessness, freedom from irritating qualities, and lack of pharmacological activity make it ideal for such purposes. There is, however, a tendency to assume that its purity is constant and that it can be stored, handled, and used with a minimum of care. While it is true that municipal supplies must comply with Environmental Protection Agency regulations (or comparable regulations in other countries), drinking water *must* be repurified before it can be used in pharmaceuticals. For further information on water as H_2O, see Chapter 23.

Four of the five solvent waters described in the USP are used in the preparation of parenterals or irrigations. *Purified water* must be used for all other pharmaceutical operations and, as needed, in all the tests and assays of the compendia. Purified water must meet rigid specifications for chemical purity. Such water may be prepared by distillation, by use of ion-exchange resins, or by reverse osmosis.

A wide variety of commercially available stills are used to produce distilled water. The end use of the product dictates the size of the still and extent of pretreatment of the drinking water introduced into the system. Such water may be sterile provided the condenser is sterile, but to be called sterile, it must be subjected to a satisfactory sterilization process. However, it has been shown that *P. aeruginosa* (and other microorganisms) can grow in the distilled water produced in hospitals. The implications of this are obvious. Sterile water may be sterile at the time of production but may lose this characteristic if it is improperly stored. Hickman *et al.*,[3] by regrouping the components of conventional distillation equipment, have described a method for the continuous supply of sterile, ultrapure water.

The major impurities in water are calcium, iron, magnesium, manganese, silica, and sodium. The cations are usually combined with the bicarbonate, sulfate, or chloride anions. "Hard" waters are those that contain the calcium and magnesium cations. Bicarbonates are the major impurity in the "alkaline" waters.

Ion-exchange (deionization, demineralization) processes will efficiently and economically remove most of the major impurities in water. A cation exchanger, H_2R, first converts bicarbonates, sulfates, and chlorides to their respective acids.

$$\left.\begin{matrix} CaSO_4 \\ MgSO_4 \\ Na_2SO_4 \end{matrix}\right| + H_2R \rightarrow \left|\begin{matrix} Ca \\ Mg \\ Na_2 \end{matrix}\right. R + H_2SO_4$$

$$\left.\begin{matrix} Ca(HCO_3)_2 \\ Mg(HCO_3)_2 \\ 2NaHCO_3 \end{matrix}\right| + H_2R \rightarrow \left|\begin{matrix} Ca \\ Mg \\ Na_2 \end{matrix}\right. R + 2H_2CO_3$$

Carbonic acid decomposes to carbon dioxide (which is removed by aeration in the decarbonator) and water.

The anion exchanger unit may contain either a weakly basic or a strongly basic anion resin. These resins adsorb sulfuric, hydrochloric, and nitric acids. Chemical reactions may involve complete adsorption or an exchange with some other anion.

$$H_2SO_4 + A \rightarrow A \cdot H_2SO_4$$

If the resin contains a hydroxyl radical, water is formed during the purification process.

$$H_2SO_4 + 2AOH \rightarrow A_2SO_4 + 2H_2O$$

Weakly dissociated carbonic and silicic acids can be removed only by strongly basic anion resins.

$$H_2SiO_3 + 2AOH \rightarrow A_2SiO_2 + 2H_2O$$

Unit capacity varies with the nature of the installation but it is possible to process as much as 15,000 gal of water/min.

Deionization processes do not necessarily produce *Purified Water* which will comply with US EPA requirements for drinking water. Resin columns retain phosphates and organic debris. Either alone or in combination, these substances can act as growth media for microorganisms. Observations have shown that deionized water containing 90 organisms/ml contained, after 24 hours storage, 10^6 organisms/ml. Columns can be partially cleaned of pseudomonads by recharging but a 0.25% solution of formaldehyde will destroy most bacteria. The column must be thoroughly washed and checked for the absence of aldehyde (by use of Schiffs Reagent) before it can be used to generate deionized water.

Ultraviolet radiant engery (240–280 nm), heat, or filtration can be used to remove or kill the microorganisms present in the water. However, the effectiveness of the latter method does not appear to equal that inherent in the use of commercially available filtration systems (e.g., Millipore Filtration). A somewhat different approach to the production of "pure" water has been described by Taylor *et al.*[4] These researchers formed stable, water-insoluble combinations by using strongly basic anion-exchange resins and triiodide ions. This "disinfectant" easily killed 3.0×10^5 *E. coli*/ml of water when passed through a column containing 3.8 g of the resin combination. The cells are not filtered from the water. They appear in the effluent but in a nonviable form.

The phenomenon of osmosis involves the passage of water from a dilute solution across a semipermeable membrane into a more concentrated solution. Flow of water can be stopped by applying pressure, equal to the osmotic pressure, to the concentrated solution. The flow of water can be reversed by applying a pressure, greater than the osmotic pressure. The process of reverse osmosis utilizes the latter principle by applying pressure, greater than the osmotic pressure, to a concentrated solution, e.g., tap water, pure water may be obtained (see *Reverse Osmosis* in Chapter 77, also Fig. 7 in the same chapter).

Cellulose acetate is used in the manufacture of semipermeable membranes for purifying water by reverse osmosis. This polymer has functional groups that can hydrogen bond to water or other substances such as alcohol. The water molecules which enter the polymer are transported from one bonding site to the next under pressure. Because of the

layer of pure water strongly adsorbed at the surface of the membrane, salts, to a large extent, are repelled from the surface, the higher-valent ions being repelled to a greater extent, thus causing a separation of ions from the water. Organic molecules are rejected on the basis of a sieve mechanism related to their size and shape. Small organic molecules, with a molecular weight smaller than approximately 200, will pass through the membrane material. Since there are few organic molecules with a molecular weight of less than 200 in the municipal water supply, reverse osmosis is usually sufficient for the removal of organic material. The pore sizes of the selectively permeable reverse osmosis membranes are between 5 Å and 100 Å. Viruses and bacteria larger than 100 Å are rejected if no imperfections exist in the membrane. The membranes have and do develop openings which permit the passage of microorganisms. Because of the semistatic conditions, bacteria can grow both upstream and downstream of the membrane.

Aromatic Waters

Aromatic waters, known also as medicated waters, are clear, saturated aqueous solutions of volatile oils or other aromatic or volatile substances. Their odors and tastes are similar to those of the drugs or volatile substances from which they are prepared, and the preparations should be free from empyreumatic (smoke-like) and other foreign odors. They are used principally as flavored or perfumed vehicles. The volatile substances from which aromatic waters are to be made should be of pharmacopeial quality or, in the case of nonofficial preparations, of the best quality if the finest flavors are to be obtained.

Aromatic waters may be prepared by one of two official processes.

Distillation—Distillation represents the most ancient and frequently the most satisfactory method for making this class of preparations. However, it is the slowest and the more expensive of the two methods.

Different authorities give different directions for the preparation of aromatic waters by distillation. For fresh drugs the proportions range from one part of drug to two of distillate, to two parts of drug to one part of distillate. For dried drugs such as cinnamon, anise, dill, caraway, and fennel the proportion is one part of drug to ten parts of distillate. In the case of dried leaf drugs such as peppermint, the proportion is three parts of drug to ten parts of distillate. Metallic distillation apparatus is usually employed, sometimes using a current of steam passed through the still. The drug should be contused or coarsely ground and combined with a sufficient quantity of *Purified Water*. On completion of the distillation process, any excess of oil in the distillate is removed and, if necessary, the clear water portion is filtered. Most distilled aromatic waters acquire an unpleasant empyreumatic odor as soon as they are distilled. This passes off gradually on exposure to air, if care has been taken not to expose the drug to direct heat during distillation. If precautions are not taken to protect the drug from partial burning, the odor of the carbonized substance will be noticeable in the distilled aromatic water. To avoid this difficulty, the drug should be placed in a partially filled round-bottomed copper wire cage, which is placed in the still to thus avoid any contact of the substance with the heated surface. The meshes of the cage are coarse enough to permit free passage of vapors and boiling water. If the volatile principles in the water are delicate and present in small quantities (e.g., as in orange flower and rose waters), the distillate is returned several times to the still with fresh portions of flowers, thus giving rise to the commercial terms *double distilled, triple distilled,* or *quadruple distilled,* according to the number of redistillations. This process is called *cohobation.*

Stronger Rose Water is an example of an aromatic water prepared by distillation. It acquires a musty odor when stored in tightly closed containers over long periods of time. The odor of this water is best preserved by allowing limited access of fresh air to the container. Cotton plugs exclude foreign matter but, at the same time, permit air to enter the container. Stronger Rose Water, diluted with an equal volume of purified water, may be used when *Rose Water* is specified in a formulation.

Solution—Aromatic waters may be prepared by repeatedly shaking 2 g or 2 ml (if a liquid) of the volatile substance with 1000 ml of purified water. The mixture is set aside for 12 hours, filtered through wetted filter paper, and made to volume (1000 ml) by adding purified water through the filter.

In terms of time and equipment this method is more convenient than that described above. However, making medicated waters by agitation with an excess of volatile oil, permitting the excess to remain and drawing off the water as required, is not recommended. Volatile oils may deteriorate through exposure to light and air and, because of this, may yield unsatisfactory aromatic waters.

Certain waters are prepared by dissolving well-defined substances in purified water. Camphor water is a saturated solution of camphor in purified water. Chloroform water is prepared by adding enough chloroform to purified water (in a dark amber-colored bottle) to maintain a slight excess after the mixture has been thoroughly agitated. The latter water has been used as a sedative in cough, asthma, and colic mixtures and as a vehicle for administering active ingredients.

Aromatic waters may also be prepared by thoroughly incorporating the volatile oil with 15 g of talc or with a sufficient quantity of purified siliceous earth or pulped filter paper. Purified water (1000 ml) is added and the mixture is agitated for 10 min. The water is then filtered (and, if necessary, refiltered) and its volume adjusted to 1000 ml by passing purified water through the filter.

This is the process most frequently employed since the water can be prepared promptly, only 10 minutes of agitation being required. The use of talc, purified siliceous earth, or pulped filter paper greatly increases the surface of the volatile substance, insuring more rapid saturation of the water. These dispersing substances also form an efficient filter bed which produces a clear solution. They are also unreactive.

Other methods have been suggested for the preparation of aromatic waters. These are based on use of soluble concentrates or on incorporation of solubilizing agents such as polysorbate 20 or Tween 20 (*Atlas*). However, such preparations are susceptible to mold growth and, in concentrations higher than 2%, impart an objectionable oily taste.

Concentrated waters (e.g., peppermint, dill, cinnamon, caraway, and anise) may be prepared in the following manner.

Dissolve 20 ml of the volatile oil in 600 ml of 90% ethanol. Add sufficient purified water in successive small portions to produce 1000 ml solution. Shake vigorously after each addition. Add 50 g of sterilized purified talc, shake occasionally for several hours, and filter.

If anise concentrate is being prepared, the volume of ethanol must be increased to 700 ml.

The aromatic water is prepared by diluting the concentrate with 39 times its volume of water. In general, these methods yield aromatic waters that are slightly inferior in quality to those prepared by distillation or solution.

The chemical composition of many of the volatile oils used in the preparation of pharmaceuticals and cosmetics is now known. Similarly, many synthetic aromatic substances have a characteristic odor. For example, geranyl phenyl acetate has a honey odor. Such substances, either alone or in combination, can be used in nonofficial preparations and, by combining them in definite proportions, it is possible to pro-

duce substitutes for the officially recognized oil. Imitation Otto Rose (which contains phenylethyl alcohol, rhodinol, citronellol, and other ingredients) is an example of the types of substitutes which are now available.

Incompatibilities—The principal difficulty experienced in the compounding of prescriptions containing aromatic waters is due to a "salting out" action of certain ingredients, such as very soluble salts, on the volatile principle of the aromatic water. A replacement of part of the aromatic water with purified water is permissible when no other function is being served than that of a vehicle. Otherwise a dilution of the product with a suitable increase in dosage is indicated. It has been suggested that this salting out action of soluble salts may be used in the evaluation of aromatic waters. The method is based on the determination of the amount of standard sodium citrate solution required to produce cloudiness in the aromatic water.

Preservation—Aromatic waters will deteriorate with time and should, therefore, be made in small quantities and protected from intense light and excessive heat, and stored in airtight, light-resistant containers. Deterioration may be due to volatilization, decomposition, or mold growth and will produce solutions that are cloudy and have lost all traces of their agreeable odor. Distilled water is usually contaminated with mold-producing organisms. *Recently* distilled and boiled water should, therefore, be used in the preparation of medicated waters. No preservative should be added to medicated waters. If they become cloudy or otherwise deteriorate, they should be discarded.

Aqueous Acids

The official inorganic acids and certain organic acids, although of minor significance as therapeutic agents, are of great importance in chemical and pharmaceutical manufacturing. This is especially true of acetic, hydrochloric, nitric, and sulfuric acids. The three latter acids, because of their relative completeness of ionization, are termed strong acids. These acids, and especially the latter two, are very caustic and corrosive.

The inorganic acids are generally divided into two groups: (1) the *hydracids*, which contain no oxygen, e.g., hydriodic, hydrobromic, hydrochloric, and hydrofluoric acids and (2) the oxygen-containing acids, e.g., hypophosphorous, nitric, phosphoric, and sulfuric acids.

Percentage Strengths—Many of the more important inorganic acids are available commercially in the form of concentrated aqueous solutions. The percentage strength varies from one acid to another and depends on the solubility and stability of the solute in water and on the manufacturing process. Thus, the official Hydrochloric Acid contains from 36.5 to 38% by weight of HCl, whereas Nitric Acid contains from 69 to 71% by weight of HNO_3, and Sulfuric Acid contains from 95 to 98% by weight of H_2SO_4.

Because the strengths of these concentrated acids are stated in terms of % by weight, it is essential that specific gravities also be provided if one is to be able to calculate conveniently the amount of absolute acid contained in a unit volume of the solution as purchased. The mathematical relationship involved is given by the equation $M = V \times S \times F$, wherein M is the mass in g of absolute acid contained in V ml of solution having a specific gravity S and a fractional percentage strength F. As an example, Hydrochloric Acid containing 36.93% by weight of HCl has a specific gravity of 1.1875. Therefore, the amount of absolute HCl supplied by 100 ml of this hydrochloric acid solution is given by:

$$M = 100 \times 1.1875 \times 0.3693 = 43.85 \text{ g HCl}$$

Commercially, the specific gravities of liquids are often given on the arbitrary Baumé scale. In instances where this is the only kind of specific gravity data provided, it is necessary first to calculate the true specific gravity from the Baumé degree figure. Tables relating the percentage strengths of acids to specific gravity and to the Baumé degree are usually provided in handbooks of chemistry and physics.

Incompatibilities—Although many of the reactions characteristic of acids offer opportunities for incompatibilities, only a few are of sufficient importance to require more than casual mention. Acids and acid salts decompose carbonates with liberation of carbon dioxide and, in a closed container, sufficient pressure may be developed to produce an explosion. Inorganic acids react with salts of organic acids to produce the free organic acid and a salt of the inorganic acid. If insoluble, the organic acid will be precipitated. Thus, salicylic acid and benzoic acid are precipitated from solutions of salicylates and benzoates. Boric acid is likewise precipitated from concentrated solutions of borates. By a similar reaction, certain soluble organic compounds are converted into an insoluble form. Sodium phenobarbital, for example, is converted into phenobarbital which in aqueous solution will precipitate.

The ability of acids to combine with alkaloids and other organic compounds containing a basic nitrogen atom is utilized in preparing soluble salts of these substances.

It should be borne in mind that certain solutions, syrups, elixirs, and other pharmaceutical preparations may contain free acid which causes these preparations to exhibit the incompatibilities of the acid.

Acids also possess the incompatibilities of the anions which they contain, and in the case of organic acids, these are frequently of prime importance. These are discussed under the specific anions.

Diluted Acids—The diluted acids in the US are aqueous solutions of acids, of a suitable strength (usually 10% *w/v* but Diluted Acetic Acid is 6% *w/v*) for internal administration or for the manufacture of other preparations.

The strengths of the official undiluted acids are expressed as percentages weight in weight whereas the strengths of the official diluted acids are expressed as percentages weight in volume. It therefore becomes necessary to consider the specific gravities of the concentrated acids when calculating the volume required to make a given quantity of diluted acid. The following equation will give the number of ml required to make 1000 ml of diluted acid:

$$\frac{\text{Strength of diluted acid} \times 1000}{\text{Strength of undiluted acid} \times \text{sp gr of undiluted acid}}$$

Thus, if one wishes to make 1000 ml of Diluted Hydrochloric Acid USP using Hydrochloric Acid which assays 37.5% HCl (sp gr 1.18), the amount required is

$$\frac{10 \times 1000}{37.5 \times 1.18} = 226 \text{ ml}$$

One of these diluted acids, Diluted Hydrochloric Acid USP is used in the treatment of achlorhydria. However, it may irritate the mucous membrane of the mouth and attack the enamel of the teeth. The usual dose is 5 ml, well diluted with water. In the treatment of achlorhydria no attempt is made to administer more than a relief-producing dose. The normal pH of the gastric juice is 0.9 to 1.5 and, in order to attain this level, particularly in severe cases of gastric malfunction, somewhat larger doses of the acid would be required.

Solutions

A solution is a liquid preparation that contains one or more soluble chemical substances dissolved in water. The solute is usually nonvolatile. Solutions are used for the specific therapeutic effect of the solute, either internally or externally. Although the emphasis here is on the aqueous solution, certain

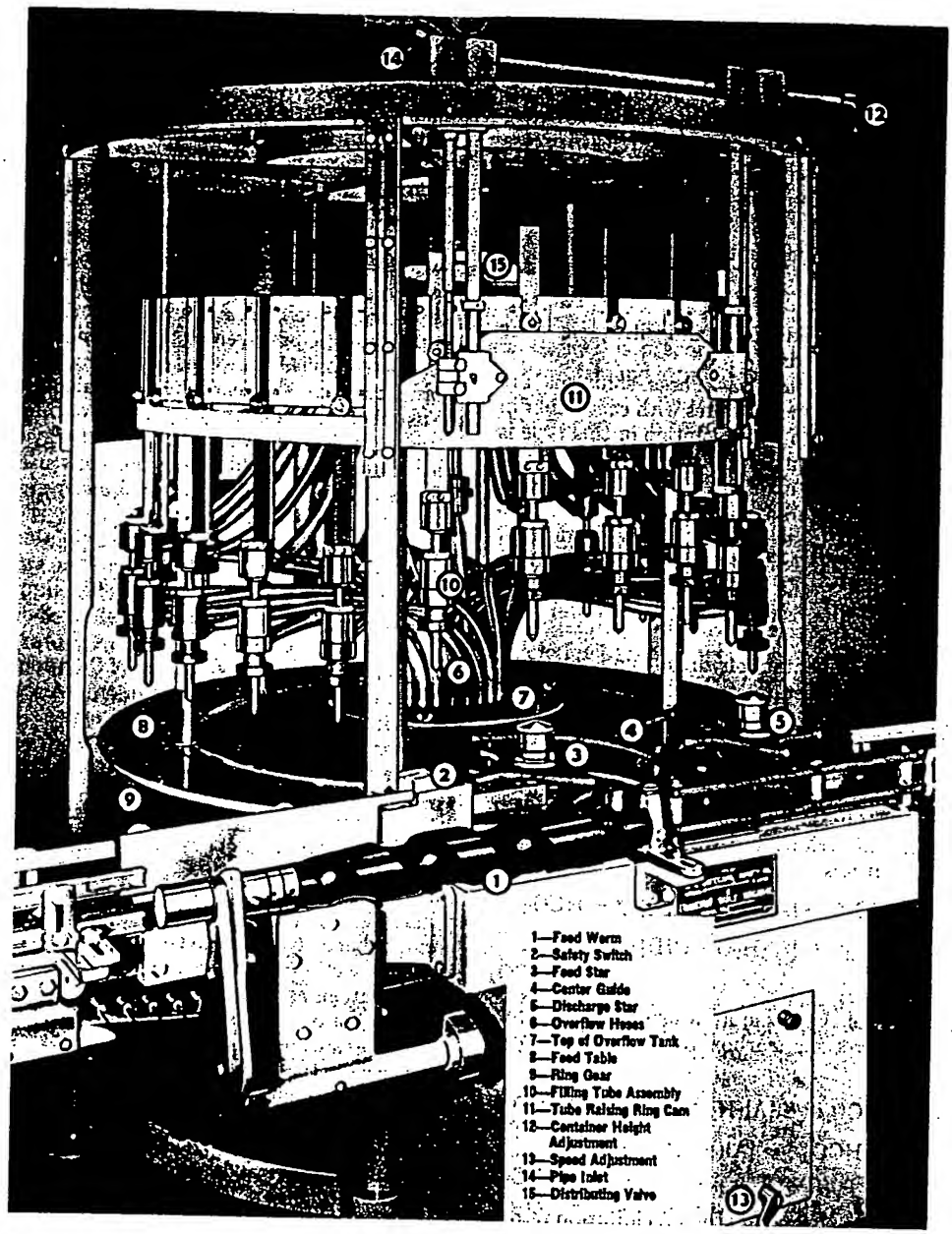


Fig. 83-1. A rotary gravity bottle filler (courtesy, US Bottlers).

ations of this type (syrups, infusions, and decoctions) istinctive characteristics and are, therefore, described ere.

ents, solubility, and general methods for the incorpo- of a solute in a solvent are discussed in Chapter 16. ns are usually bottled automatically by utilizing nent of the type shown in Fig. 83-1.

paration—A specific method of preparation is given compendia for most solutions. These procedures fall ree main categories.

ple Solutions—Solutions of this type are prepared by ing the solute in a suitable solvent. The solvent may other ingredients which stabilize or solubilize the ingredient. Calcium Hydroxide Topical Solution Water), Sodium Phosphate Solution, and Strong Iodide n are examples of solutions that are prepared in this

ium Hydroxide Topical Solution contains, in each 100 less than 140 mg of $Ca(OH)_2$. The solution is prepared rously agitating 3 g of calcium hydroxide with 1000 ml cool, purified water. Excess calcium hydroxide is allowed to settle out and the clear, supernatant liquid is dispensed.

An increase in solvent temperature usually implies an increase in solute solubility. This rule does not apply, however, to the solubility of calcium hydroxide in water, which decreases with increase in temperature. The official solution is prepared at a temperature of 25°C.

Solutions containing hydroxides react with the carbon dioxide in the atmosphere.

$$OH^- + CO_2 \rightarrow HCO_3^-$$

$$OH^- + HCO_3^- \rightarrow CO_3^{=} + H_2O$$

$$Ca^{++} + CO_3^{=} \rightarrow CaCO_3$$

Calcium Hydroxide Topical Solution should, therefore, be preserved in well-filled, tight containers, at a temperature not exceeding 25°C.

Strong Iodine Solution contains, in each 100 ml, 4.5–5.5 g of iodine, and 9.5–10.5 g of potassium iodide. It is prepared by dissolving 50 g of iodine in 100 ml of purified water con-

taining 100 g of potassium iodide. Sufficient purified water is then added to make 1000 ml of solution.

One g of iodine dissolves in 2950 ml of water. However, solutions of iodides dissolve large quantities of iodine. Strong Iodine Solution is, therefore, a solution of polyiodides in excess iodide.

$$I^- + nI_2 \rightarrow I^-_{(2n+1)}$$

Doubly charged anions may be found also

$$2I^- + nI_2 \rightarrow I^-_{(2n+2)}$$

Strong Iodine Solution is classified as an antigoitrogenic. The usual dose is 0.3 ml 3 times a day.

Solution by Chemical Reaction—These solutions are prepared by reacting two or more solutes with each other in a suitable solvent. An example of a solution of this type is Aluminum Subacetate Topical Solution.

Aluminum sulfate (145 g) is dissolved in 600 ml of cold water. The solution is filtered and precipitated calcium carbonate (70 g) is added, in several portions, with constant stirring. Acetic acid (160 ml) is slowly added and the mixture is set aside for 24 hours. The product is filtered and the magma on the Büchner filter is washed with cold water until the total filtrate measures 1000 ml.

The solution contains pentaquohydroxo- and tetraquodihydroxoaluminum (III) acetates and sulfates dissolved in an aqueous medium saturated with calcium sulfate. The solution contains a small amount of acetic acid. It is stabilized by the addition of not more than 0.9% boric acid.

The reactions involved in the preparation of the solution are given below. The hexaquo aluminum cations are first converted to the nonirritating $[Al(H_2O)_5(OH)]^{++}$ and $[Al(H_2O)_4(OH)_2]^+$ cations.

$$[Al(H_2O)_6]^{+++} + CO_3^= \rightarrow [Al(H_2O)_5(OH)]^{++} + HCO_3^-$$

$$[Al(H_2O)_6]^{+++} + HCO_3^- \rightarrow [Al(H_2O)_5(OH)]^{++} + H_2O + CO_2$$

As the concentration of the hexaquo cations decreases, secondary reactions involving carbonate and bicarbonate occur.

$$[Al(H_2O)_5(OH)]^{++} + CO_3^= \rightarrow [Al(H_2O)_4(OH)_2]^+ + HCO_3^-$$

$$[Al(H_2O)_5(OH)]^{++} + HCO_3^- \rightarrow [Al(H_2O)_4(OH)_2]^+ + H_2CO_3$$

The pH of the solution now favors the precipitation of dissolved calcium ions as the insoluble sulfate. Acetic acid is now added. The bicarbonate which is formed in the final stages of the procedure is removed as carbon dioxide.

Aluminum Subacetate Topical Solution is used in the preparation of Aluminum Acetate Solution (Burow's Solution). The latter solution contains 15 ml of glacial acetic acid, 545 ml of Aluminum Subacetate Solution, and sufficient water to make 1000 ml. It is defined as a solution of aluminum acetate in approximately 5%, by weight, of acetic acid in water. It is stabilized by the addition of not more than 0.6% boric acid.

Solution by Extraction—Drugs or pharmaceutical necessities of vegetable or animal origin are often extracted with water or with water containing other substances. Preparations of this type may be classified as solutions but, more often, are classified as extractives.

Douches

A douche is an aqueous solution directed against a part or into a cavity of the body. It functions as a cleansing agent or antiseptic agent. An *eye douche*, used to remove foreign particles and discharges from the eyes, is directed gently at an oblique angle and is allowed to run from the inner to the outer corner of the eye. *Pharyngeal douches* are used to prepare the interior of the throat for an operation and to cleanse it in suppurative conditions. Similarly, there are *nasal douches* and *vaginal douches*. Douches are usually directed to the appropriate body part by using bulb syringes. These are described in Chapter 103.

Douches are most frequently dispensed in the form of a powder with directions for dissolving in a specified quantity of water, usually warm. However, tablets for preparing solutions are available (e.g., Dobell's Solution Tablets) or the solution may be prepared by the pharmacist. If powders or tablets are supplied, they must be free from insoluble material, in order to produce a clear solution. Tablets are produced by the usual processes but any lubricants or diluents used must be readily soluble in water. Boric acid may be used as a lubricant and sodium chloride is normally used as a diluent. Tablets deteriorate on exposure to moist air and should be stored in airtight containers.

Preparations of this type may contain alum, zinc sulfate, boric acid, phenol, or sodium borate. The ingredients in one douche are alum (4 g), zinc sulfate (4 g), liquefied phenol (5 ml), glycerin (125 ml), and water (a sufficient quantity to make 1000 ml of solution). Sodium borate (borax, sodium tetraborate) is used in the preparation of Compound Sodium Borate Solution NF XI (Dobell's Solution). A solution of sodium borate in water is alkaline to litmus paper. In the presence of water, sodium metaborate, boric acid, and sodium hydroxide are formed.

$$Na_2B_4O_7 + 3H_2O \rightarrow 2NaBO_2 + 2H_3BO_3$$

$$NaBO_2 + 2H_2O \rightarrow NaOH + H_3BO_3$$

The official solution contains sodium borate, sodium bicarbonate, liquefied phenol, and glycerin. The reaction between boric acid and glycerin is given in the section on *Washes*. See also the section on *Honeys* for a discussion on the toxic manifestations associated with the topical application of boric acid and borax.

Douches are not official as a class of preparations but several substances in the compendia are frequently employed as such in weak solutions, e.g., Benzalkonium Chloride is used in various douches and Compound Sodium Borate Solution is used as a nasal or pharyngeal douche.

Vaginal or urethral douches are occasionally referred to as Irrigations. These solutions may have an antiseptic, astringent, or soothing action and are prepared immediately before use by dissolving the medicament in the required amount of water. One example of such a preparation is Irrigation of Lactic Acid BPC 1963. This solution contains 3.75 ml of lactic acid in every 600 ml of aqueous product. Note that *Sterile Water for Irrigation* is described in the USP.

Enemas

Enemas are rectal injections employed to evacuate the bowel, to influence the general system by absorption, or to affect locally the seat of disease. They may possess anthelmintic, nutritive, sedative, or stimulating properties, or they may contain radiopaque substances for roentgenographic examination of the lower bowel. Some official enemas are those of aminophylline, hydrocortisone, and methylprednisolone acetate. Enemas are usually given at body temperature in quantities of 1 to 2 pt injected slowly with a syringe. If they are to be retained in the intestine, they should not be used in larger quantities than 6 fluid ounces for an adult.

Starch enema may be used either by itself or as a vehicle for other forms of medication. A thin paste is made by triturating 30 g of powdered starch with 200 ml of cold water. Sufficient

boiling water is added to make 1000 ml of enema. The preparation is then reheated to obtain a transparent liquid.

Barium sulfate enema contains 120 g of barium sulfate, 100 ml of acacia mucilage, and sufficient starch enema to make 500 ml.

Sodium chloride, sodium bicarbonate, sodium monohydrogen phosphate, and sodium dihydrogen phosphate are used in enemas. These substances may be used alone, in combination with each other, or in combination with irritants such as soap. Enema of Soap BPC 1963 is prepared by dissolving 50 g of soft soap in sufficient purified water to make 1000 ml of enema. Fleet Enema, a commercially available enema containing 16 g of sodium acid phosphate and 6 g of sodium phosphate in 100 ml, is marketed as a single-dose disposable unit.

Gargles

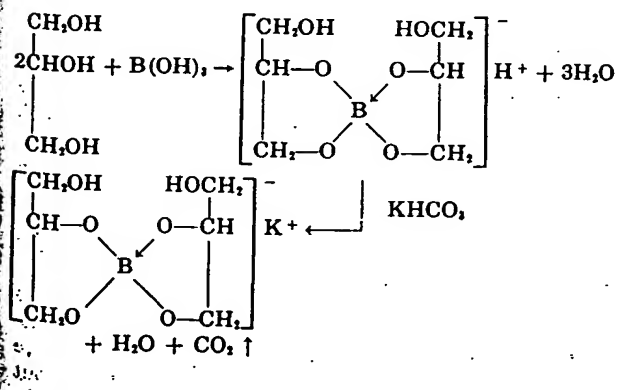
Gargles are aqueous solutions used for treating the pharynx and nasopharynx by forcing air from the lungs through the gargle which is held in the throat. Many gargles must be diluted with water prior to use. Although mouthwashes are considered as a separate class of pharmaceuticals, many are used as gargles, either as is or diluted with water.

Phenol Gargle, and Potassium Chlorate and Phenol Gargle are official in the BPC. The former gargle contains 50 ml of phenol glycerin (16% *w/w* phenol and 84% *w/w* glycerin), 10 ml of amaranth solution (1% *w/v* in chloroform water), and water to make 1000 ml. This gargle should be diluted with an equal volume of warm water before use. The product should be so labeled that it cannot be mistaken for preparations intended for internal administration.

Washes

A mouthwash is an aqueous solution which is most often used for its deodorant, refreshing, or antiseptic effect. It may contain alcohol, glycerin, synthetic sweeteners, and surface-active, flavoring, and coloring agents. Commercial preparations contain such local anti-infective agents as hexetidine and cetylpyridinium chloride. They may be either acidic or basic in reaction and, in some instances, are fairly effective in reducing bacterial concentrations and odors in the mouth for short periods of time.

The products of commerce (e.g., Cepacol, Listerine, Micrin, Scope, etc.) vary widely in composition. Compound Sodium Borate Solution NF XI (Dobell's Solution) is used as an antiseptic wash. Antiseptic Solution and Mouthwash are described in NF XII. The latter wash contains sodium borate, glycerin, and potassium bicarbonate. The reactions which take place when these substances are dissolved in water are given below.



Compound Sodium Chloride Mouthwash, and Zinc Sulphate and Zinc Chloride Mouthwash are described in the BPC. The former wash contains sodium chloride, sodium bicarbonate, concentrated peppermint emulsion, and double-strength chloroform water; the latter, zinc sulfate, zinc chloride, compound tartrazine solution, dilute hydrochloric acid, and double-strength chloroform water.

Juices

A juice is prepared from fresh ripe fruit, is aqueous in character, and is used in making syrups which are employed as vehicles. The freshly expressed juice is preserved with benzoic acid, and is allowed to stand at room temperature for several days, until the pectins which are naturally present are destroyed by enzymatic action, as indicated by the filtered juice yielding a clear solution with alcohol. Pectins, if allowed to remain, would cause precipitation in the final syrup.

Cherry Juice is described in the USP, and Raspberry Juice in USP XVIII. Concentrated Raspberry Juice BPC is prepared from the clarified juice of raspberries. Pectinase is stirred into pulped raspberries and the mixture is allowed to stand for 12 hours. The pulp is pressed, the juice is clarified, and sufficient sucrose is added to adjust the weight per ml at 20°C to 1.050–1.060 g. The juice is then concentrated to one-sixth of its original volume. Sufficient sulfurous acid or sodium metabisulfite is added to preserve the juice.

Artificial flavors have now replaced many of the natural fruit juices. Although they lack the flavor of the natural juice, they are more stable and are easier to incorporate into the final pharmaceutical form.

Sprays

Sprays are solutions of various drugs in aqueous vehicles and are applied to the mucous membrane of the nose and the throat by means of an atomizer or nebulizer. The spray device should produce relatively coarse droplets if the action of the drug is to be restricted to the upper respiratory tract. Fine droplets tend to penetrate farther into the respiratory tract than is desirable.

Many of the older sprays were prepared by dissolving various drugs in light liquid petrolatum. This vehicle may retard normal ciliary activity on the nasal mucosa and, if drops of oil enter the trachea, can cause lipoid pneumonia. On the basis of such observations, aqueous sprays, which are isotonic with nasal secretions and of approximately the same pH, are preferred. Such sprays may contain antibiotics, antihistamines, vasoconstrictors, alcohol, and suitable solubilizing and wetting agents. The pharmacist will handle many commercial preparations that comply with the basic definition given above and that help to alleviate the nasal congestion due to the common cold. For example, one of these contains chlorpheniramine maleate, phenylephrine hydrochloride, and gramicidin. Another is described as an isotonic, buffered (pH 6.2), aqueous solution containing phenylephrine hydrochloride, phenylpropranolamine hydrochloride, pheniramine maleate, and chlorobutanol. Most of the highly advertised sprays are marketed either in standard dropper bottles or in plastic squeeze units.

A number of nasal solutions official in USP, e.g., naphazoline hydrochloride and phenylephrine hydrochloride, are available commercially as sprays.

Sweet or Other Viscid Aqueous Solutions

Solutions which are sweet or viscid include Syrups, Honeys, Mucilages, and Jellies. All of these preparations are viscous liquids or semisolids. The basic sweet or viscid substances giving body to these preparations are sugars, polyols, or polysaccharides (gums).

Syrups

Syrups are concentrated solutions of a sugar such as sucrose in water or other aqueous liquid. When purified water alone is used in making the solution of sucrose, the preparation is known as *syrup*, or *simple syrup*. In addition to sucrose, certain other polyols, such as glycerin or sorbitol, may be added to retard crystallization of sucrose or to increase the solubility of added ingredients. When the aqueous preparation contains some added medicinal substance, the syrup is called a *medicated* syrup. A *flavored* syrup is one which is usually not medicated, but which contains various aromatic or pleasantly flavored substances and is intended to be used as a vehicle or flavor for prescriptions.

Flavored syrups offer unusual opportunities as vehicles in extemporaneous compounding and are readily accepted by both children and adults. Because they contain no or very little alcohol, they are vehicles of choice for many of the drugs that are prescribed by pediatricians. Their lack of alcohol makes them superior solvents for water-soluble substances.

Syrups possess remarkable masking properties for bitter and saline drugs. Glycyrrhiza Syrup has been recommended for disguising the salty taste of bromides, iodides, and chlorides. This has been attributed to its colloidal character and to its double sweetness—the immediate sweetness of the sugar and the lingering sweetness of the glycyrrhizin. This syrup is also of value in masking bitterness in preparations containing the B complex vitamins. Acacia Syrup, because of its colloidal character, is of particular value as a vehicle for masking the disagreeable taste of many medicaments. Raspberry Syrup is one of the most efficient flavoring agents and is especially useful in masking the taste of bitter drugs. Many factors, however, enter into the choice of a suitable flavoring agent. Literature reports are often contradictory and there appears to be no substitute for the taste panel. The literature on this subject has been reviewed by Meer,[5] and this reference and Chapter 67 should be consulted for further information on the flavoring of pharmaceuticals.

In manufacturing syrups the sucrose must be carefully selected and a purified water, free from foreign substances, and clean vessels and containers must be used. The operation must be conducted with care so as to avoid contamination, if the products are to be stable preparations.

It is important that the concentration of sucrose approach but not quite reach the saturation point. In dilute solutions sucrose provides an excellent nutrient for molds, yeasts, and other microorganisms. In concentrations of 65% by weight or more, the solution will retard the growth of such microorganisms. However, a saturated solution may lead to crystallization of a part of the sucrose under conditions of changing temperature.

When heat is used in the preparation of syrups, there is almost certain to be an inversion of a slight portion of the sucrose.

$$\underset{\text{Sucrose}}{C_{12}H_{22}O_{11}} + H_2O \rightarrow 2\underset{\text{Invert sugar}}{C_6H_{12}O_6}$$

Sucrose solutions rotate polarized light to the right but, as hydrolysis proceeds, the optical rotation decreases and becomes negative when the reaction is complete. This reaction is termed *inversion* because *invert sugar* (dextrose plus levulose) is formed. The speed of inversion is greatly increased by the presence of acids; the hydrogen ion acts as a catalyst in this hydrolytic reaction. Invert sugar is more readily fermentable than sucrose and tends to darken in color. Nevertheless its two reducing sugars are of value in retarding the oxidation of other substances.

Invert Syrup is described in the BPC. The syrup is prepared by hydrolyzing sucrose with hydrochloric acid and neutralizing the solution with calcium or sodium carbonate. The sucrose in the 66.7% *w/w* solution must be at least 95% inverted. The monograph states that invert syrup, when mixed in suitable proportions with syrup, prevents the deposition of crystals of sucrose under most conditions of storage.

The levulose formed during inversion is sweeter than sucrose and therefore the resulting syrup is sweeter than the original syrup. The relative sweetness of levulose, sucrose, and dextrose is in the ratio 173:100:74. Thus invert sugar is $1/100\ (173 + 74)^{1/2} = 1.23$ times as sweet as sucrose. The levulose formed during the hydrolysis is also responsible for the darkening of syrup. It is sensitive to heat and darkens readily, particularly in solution. When syrup or sucrose is overheated, it caramelizes. See *Caramel* (page 1229).

Preparation—Syrups are prepared in various ways, the choice of the proper method depending on the physical and chemical characteristics of the substances entering into the preparation. Four methods which are employed may be summarized as follows: (1) solution with heat; (2) agitation without heat; (3) addition of a medicating liquid to syrup; and (4) percolation.

Solution with Heat—This is the usual method of making syrups when the valuable constituent is neither volatile nor injured by heat, and when it is desirable to make the syrup rapidly. The sucrose is usually added to the purified water or aqueous solution and heated until solution is effected, then strained, and sufficient purified water added to make the desired weight or volume. If the syrup is made from an infusion, a decoction, or an aqueous solution containing organic matter, it is usually proper to heat the syrup to the boiling point to coagulate albuminous matter; this is separated subsequently by straining. If the albumin or other impurities were permitted to remain in the syrup, fermentation would probably be induced in warm weather. Saccharometers are very useful in making syrups by the hot process in cases where the proper specific gravity of the finished syrup is known. The saccharometer may be floated in the syrup while boiling, and thus the exact degree of concentration determined without waiting to cool the syrup and having to heat it again to concentrate it further. When taking a reading of the specific gravity of the hot syrup allowance must be made for the variation from the official temperature (specific gravities in the USP are taken at 25°C).

Excessive heating of syrups at the boiling temperature is undesirable since more or less inversion of the sucrose occurs with an increased tendency to ferment. Syrups cannot be sterilized in an autoclave without some caramelization. This is indicated by a yellowish or brownish color resulting from the formation of caramel, by the action of heat upon sucrose.

The formula and procedure given for Acacia Syrup (page 1240) illustrate this method of preparation.

Agitation without Heat—This process is used in those cases where heat would cause the loss of valuable volatile constituents. In making quantities up to 2000 ml or 2 qt the sucrose should be added to the aqueous solution in a bottle of about twice the size required for the syrup. This permits active agitation and rapid solution. A "five-pint," glass-stoppered

"tincture" bottle is well adapted for the making of 1000 ml of syrup by this process. Stoppering of the bottle is important, as it prevents contamination and loss during the process. The bottle should be allowed to lie on its side when not being agitated. Glass-lined tanks with mechanical agitators, especially adapted to dissolving of sucrose, are used for making syrups in large quantities.

This method and that previously described are used for the preparation of a wide variety of preparations that are popularly described as syrups. Most cough syrups, for example, contain sucrose and one or more active ingredients. However, the exact composition of such products is not given on the label. Furthermore, some of these products are listed in the compendium but no directions are given for their preparation. For example, Guaifenesin Syrup (glyceryl guaiacolate syrup) is official but the only known ingredients are guaifenesin (glyceryl guaiacolate) and ethanol (not less than 3% or more than 4%).

The BPC, on the other hand, gives a method for the preparation of Codeine Phosphate Syrup. This product contains codeine phosphate (5 g), purified water (15 ml), chloroform spirit (25 ml), and sufficient syrup to make 1000 ml. It can be used for the relief of cough but the official cough syrup in the BPC is Codeine Linctus. This linctus is really a medicated syrup which possesses demulcent, expectorant, or sedative properties. Unlike the syrup, it is colored and flavored. The formula for Codeine Linctus BPC is:

Codeine Phosphate	3 g
Compound Tartrazine Solution	10 ml
Benzoic Acid Solution	20 ml
Chloroform Spirit	20 ml
Water	20 ml
Lemon Syrup	200 ml
Syrup	to 1000 ml

Dissolve the codeine phosphate in the water, add 500 ml of the syrup, and mix. Add the other ingredients and sufficient syrup to produce 1000 ml.

For pediatric use, 200 ml of this linctus is diluted with sufficient syrup to make 1000 ml. If sugar is contraindicated in the diet, Diabetic Codeine Linctus can be used:

Codeine Phosphate	3 g
Citric Acid	5 g
Lemon Spirit	1 ml
Compound Tartrazine Solution	10 ml
Benzoic Acid Solution	20 ml
Chloroform Spirit	20 ml
Water	20 ml
Sorbitol Solution	to 1000 ml

Dissolve the codeine phosphate and the citric acid in the water, add 750 ml of the sorbitol solution, and mix. Add the other ingredients and sufficient sorbitol solution to produce 1000 ml.

Sorbitol Solution is the sweetening agent and contains 70% *w/w* of total solids, consisting mainly of D-sorbitol. It has about half the sweetening power of syrup.

Basic formulations can easily be varied to produce the highly advertised articles of commerce. The prescription-only drug (e.g., codeine phosphate, methadone, etc.) must, of course, be omitted from the formulation but, in certain countries, such as Canada, a decreased quantity of codeine phosphate is permitted in the OTC cough syrup. In addition to the ingredients cited or listed in the official compendia (e.g., tolu, squill, ipecacuanha, etc.), many cough syrups contain an antihistamine.

Many other active ingredients (e.g., ephedrine sulfate, dicyclomine hydrochloride, chloral hydrate, chlorpromazine hydrochloride, etc.) are marketed as syrups. Like the cough syrups, these preparations are flavored and colored and are recommended in those instances where the patient cannot swallow the solid dosage form. An example of such a preparation is Ephedrine Sulfate Syrup USP XVIII. Besides the active ingredient, the syrup contains citric acid, amaranth solution, caramel, lemon and orange oils, benzaldehyde, vanillin, ethanol, and sucrose. Amaranth has been banned as an ingredient in manufactured products in a number of countries, including the US.

Addition of a Medicating Liquid to Syrup—This method is resorted to in those cases in which fluidextracts, tinctures, or other liquids are added to syrup to medicate it. Syrups made in this way usually develop precipitates since alcohol is often an ingredient of the liquids thus used, and the resinous and oily substances dissolved by the alcohol precipitate when mixed with the syrup, producing unsightly preparations. A modification of this process, frequently adopted, consists of mixing the fluidextract or tincture with the water, allowing the mixture to stand to permit the separation of insoluble constituents, filtering, and then dissolving the sucrose in the filtrate. It is obvious that this procedure is not permissible when the precipitated ingredients are the valuable medicinal agents.

The formula and procedure given for Aromatic Eriodictyon Syrup (page 1240) illustrate this method of preparation.

Percolation—In this procedure, purified water or an aqueous solution is permitted to pass slowly through a bed of crystalline sucrose, thus dissolving it and forming a syrup. A pledget of cotton is placed in the neck of the percolator and the water or aqueous solution added. By means of a suitable stopcock the flow is regulated so that drops appear in rapid succession. If necessary, a portion of the liquid is repassed through the percolator to dissolve all of the sucrose. Finally, sufficient purified water is passed through the cotton to make the required volume.

To be successful in using this process, care in several particulars must be exercised: (1) the percolator used should be cylindrical or semicylindrical, and cone-shaped as it nears the lower orifice; (2) a coarse granular sugar must be used, otherwise it will form into a compact mass, which the liquid cannot permeate; (3) the purified cotton must be introduced with care. If pressed in too tightly, it will effectually stop the process; if inserted too loosely, the liquid will pass through the cotton rapidly and the filtrate will be weak and turbid (from imperfect filtration); it should be inserted completely within the neck of the percolator, since a protruding end, inside the percolator, up through the sucrose, will permit the last portions of water to pass out at the lower orifice without dissolving all of the sucrose. For specific directions see *Syrup* (page 1240). The process of percolation is applied on a commercial scale for the making of official syrups as well as those for confectionary use.

Percolation is the preferred method for the preparation of Syrup USP (page 1240). The sucrose, in this instance, is placed in the percolator. However, a slightly modified approach must be used if a drug of vegetable origin is to be incorporated into the syrup. For example, wild cherry bark is first percolated with water; the collection vessel contains sucrose (800 g) and glycerol (50 ml). When the total volume is 1000 ml, the percolate is agitated to produce Wild Cherry Syrup BPC.

Preservation—Syrups should not be made in larger quantities than can be used within a few months, except in those cases where special facilities can be employed for their preservation. A low temperature is the best method of preservation for syrups. The USP suggests that syrups be kept at a temperature not above 25°C. Concentration without supersaturation is also a condition favorable to preservation. The USP states that syrups may contain preservatives to prevent bacterial and mold growth. Preservatives such as glycerin, methylparaben, benzoic acid, and sodium benzoate may be added, particularly when the concentration of sucrose in the syrup is low. Combinations of alkyl esters

of *p*-hydroxybenzoic acid are effective inhibitors of yeasts which have been implicated in the contamination of commercial syrups.[6] Any attempt to restore syrups which have been spoiled through fermentation by heating them and "working them over" is reprehensible.

The official syrups should be preserved in well-dried bottles, preferably those which have been sterilized. These bottles should not hold more than is likely to be required during four to six weeks and should be completely filled, carefully stoppered, and stored in a cool, dark place.

Syrups Prepared from Juices

Blackberry syrup, pineapple syrup, and strawberry syrup may be prepared by following the directions given in the BPC for Raspberry Syrup. One volume of the concentrated raspberry juice is diluted with 11 volumes of syrup. Syrup of Black Currant BPC is prepared in a similar manner but with certain modifications. The pectin in the juice is destroyed with pectinase. The syrup is prepared from 700 g of sucrose and 560 ml of clarified juice and is preserved with sulfurous acid or sodium metabisulfite. The addition of a dye is permitted, provided it complies with the pertinent government regulations.

Honeys

Honeys are thick liquid preparations somewhat allied to the syrups, differing in the use of honey, instead of syrup, as a base. They are unimportant as a class of preparations today but at one time, before sugar was available and honey was the most common sweetening agent, they were widely used. BPC lists two preparations containing honey. The first, Oxymel, or "acid honey," is a mixture of acetic acid (150 ml), purified water (150 ml), and honey (sufficient to produce 1000 ml of product). Squill Oxymel contains squill, water, acetic acid, and honey and is prepared by a maceration process.

One nonofficial preparation contains borax (10.5 g), glycerin (5.25 g), and sufficient honey to make 1000 g. It has been indicated that this type of product can cause serious boric acid intoxication in babies. In two cases mothers administered the product to the babies as teething compounds by dipping pacifiers into the Borax and Honey preparations. This resulted in seizure disorders and severe anemia. Although many cases of boric acid poisoning have been reported in the literature, direct abuse of this type prompted the Health Protection Branch of the Canadian government to prohibit the use of products containing these ingredients when intended for application to the skin of infants and children under 3 years of age.

Mucilages

The official mucilages are thick, viscid, adhesive liquids, produced by dispersing gum in water, or by extracting with water the mucilaginous principles from vegetable substances. The mucilages are all prone to decomposition, showing appreciable decrease in viscosity on storage; they should never be made in larger quantities than can be used immediately, unless a preservative is added. Acacia Mucilage NF XII contains benzoic acid and Tragacanth Mucilage BPC contains alcohol and chloroform water. Chloroform in manufactured products for internal use is banned in some countries.

The former mucilage may be prepared by placing 350 g of acacia in a graduated bottle, washing the drug with cold purified water, allowing it to drain, and adding enough warm purified water, in which 2 g of benzoic acid has been dissolved, to make the product measure 1000 ml. The bottle is then stoppered, placed on its side, rotated occasionally, and the product is strained when the acacia has dissolved.

Tragacanth Mucilage BPC is prepared by mixing 12.5 g of tragacanth with 25 ml alcohol (90%) in a dry bottle and then adding quickly sufficient chloroform water to 1000 ml and shaking vigorously. The alcohol is used to disperse the gum to prevent agglomeration on addition of the water.

Mucilages are used primarily to aid in suspending insoluble substances in liquids; their colloidal character and viscosity help them prevent immediate sedimentation. Examples include sulfur in lotions, resin in mixtures, and oils in emulsions. Both tragacanth and acacia are either partially or completely insoluble in alcohol. Tragacanth is precipitated from solution by alcohol, but acacia, on the other hand, is soluble in diluted alcoholic solutions. A 60% solution of acacia may be prepared with 20% alcohol, and a 4% solution of acacia may be prepared even with 50% alcohol.

The viscosity of tragacanth mucilage is reduced by acid, alkali, and sodium chloride, particularly if the mucilage is heated. It shows maximum viscosity at a pH of 5. Acacia is hydrolyzed by dilute mineral acids to arabinose, galactose, aldobionic and galacturonic acids. Its viscosity is low but is maintained over a wide pH range.

Several synthetic mucilage-like substances such as *polyvinyl alcohol, methylcellulose, carboxymethylcellulose,* and related substances, are used as mucilage substitutes. Methylcellulose (page 1245) is widely used as a bulk laxative since it absorbs water and swells to a hydrogel in the intestine in much the same manner as *psyllium* or *karaya gum*. The synthetic gums are nonglycogenetic and may be used in the preparation of diabetic syrups. Several formulas for such syrups, based on sodium carboxymethylcellulose, have been proposed.

Jellies

Jellies are a class of gels in which the structural coherent matrix contains a high portion of liquid, usually water. They are similar to mucilages, in that they may be prepared from gums similar to those used for mucilage, but they differ from the latter in having a jelly-like consistency. A whole gum of the best quality rather than a powdered gum is desirable in order to obtain a clear preparation of uniform consistency. Tragacanth is the gum used in the preparation of Ephedrine Sulfate Jelly NF XII. These preparations may also be formulated from acacia, chondrus, gelatin, carboxymethylcellulose, and similar substances, with water.

Jellies are used as lubricants for surgical gloves, catheters, and rectal thermometers. Lidocaine Hydrochloride Jelly USP is used as a topical anesthetic. Therapeutic vaginal jellies are available and certain jelly-like preparations are used for contraceptive purposes. The latter preparations often contain surface-active agents to enhance the spermatocidal properties of the jelly. Aromatics, such as methyl salicylate and eucalyptol, are often added to give the preparation a desirable odor.

Jellies are prone to microbial contamination and therefore contain preservatives, e.g., methyl *p*-hydroxybenzoate is used as a preservative in a base for medicated jellies. This base contains sodium alginate, glycerin, calcium gluconate, and water. The calcium ions cause a cross-linking with sodium alginate to form a gel of firmer consistency.[7]

Nonaqueous Solutions

It is difficult to evaluate fairly the importance of nonaqueous solvents in pharmaceutical processes. That they are important in the manufacture of pharmaceuticals is an understatement. However, pharmaceutical preparations, and, in particular, those intended for internal use, rarely contain more than minor quantities of the organic solvents that are common to the manufacturing or analytical operation. For example, industry uses large quantities of chloroform in some operations but the solvent is of only minor importance with respect to the final product. One ml of chloroform dissolves in about 200 ml of water and the solution so formed finds some use as a vehicle (see the section on *Aromatic Waters*). Chloroform has been an ingredient in a number of cough syrups but in some countries it has been banned in manufactured products intended for internal use. Solvents such as acetone, benzene, and petroleum ether should not be ingredients in preparations intended for internal use.

Products of commerce may contain solvents such as ethanol, glycerin, propylene glycol, certain oils, and liquid paraffin. Preparations intended for external use may contain ethanol, methanol, isopropyl alcohol, polyethylene glycols, various ethers, and certain esters. A good example of preparations of this type are the rubefacient rubbing alcohols. Rubbing Alcohol must be manufactured in accordance with the requirements of the Bureau of Alcohol, Tobacco, and Firearms, US Treasury Dept., using Formula 23-H. This mixture contains 8 parts by volume of acetone, 1.5 parts by volume of methyl isobutyl ketone, and 100 parts by volume of ethanol. Besides the alcohol in the Rubbing Alcohol, the final product must contain water, sucrose octaacetate or denatonium benzoate and may contain color additives, perfume oils, and a suitable stabilizer. The alcohol content, by volume, is not less than 68.5% and not more than 71.5%. The isopropanol content in Isopropyl Rubbing Alcohol can vary from 68.0% to 72.0% and the finished product may contain color additives, perfume oils, and suitable stabilizers.

Although the lines between aqueous and nonaqueous preparations tend to blur in those cases where the solvent is water-soluble, it is possible to categorize a number of products as nonaqueous. This section is, therefore, devoted to four groups of nonaqueous solutions; the first includes the alcoholic or hydroalcoholic solutions, examples of these being elixirs and spirits; the second, the ethereal solutions, an example being the collodions; the third, the glycerin solutions, as exemplified by the glycerites; and lastly the oleaginous solutions, as represented by the liniments, medicated oils, oleovitamins, sprays, and toothache drops.

Although the above list is self-limiting, a wide variety of solvents are used in various pharmaceutical preparations. Solvents such as glycerol formal, dimethylacetamide, and glycerol dimethylketal have been recommended for many of the products produced by the industry. However, the toxicity of many of these solvents is not well established and, for this reason, careful clinical studies should be carried out on the formulated product before it is released to the marketplace.

Collodions

Collodions are liquid preparations containing pyroxylin (a nitrocellulose) in a mixture of ethyl ether and ethanol. They are applied to the skin by means of a soft brush or other suitable applicator and, when the ether and ethanol have evaporated, leave a film of pyroxylin on the surface. The official medicated collodion, Salicylic Acid Collodion USP, contains 10% *w/v* of salicylic acid in Flexible Collodion USP and is used as a keratolytic agent in the treatment of corns and warts. Collodion USP and Flexible Collodion USP are water-repellent protectives for minor cuts and scratches. Collodion is made flexible by the addition of castor oil. Collodion has been used to reduce or eliminate the side effects of fluorouracil treatment of solar keratoses.

Elixirs

Elixirs are clear, pleasantly flavored, sweetened hydroalcoholic liquids intended for oral use. They are used as flavors and vehicles for drug substances and, when such substances are incorporated into the specified solvents, they are classified as medicated elixirs, e.g., Dexamethasone Elixir USP and Phenobarbital Elixir USP. The main ingredients in the elixir are ethanol and water but glycerin, sorbitol, propylene glycol, flavoring agents, preservatives, and syrups are often used in the preparation of the final product.

The distinction between some of the medicated syrups and elixirs is not always clear. For example, Ephedrine Sulfate Syrup USP contains 25 ml of alcohol in 1000 ml of product. Ephedrine Elixir BPC contains syrup and 100 ml of ethanol in the same final volume. Definitions are, therefore, inconsistent and, in some instances, not too important with respect to the naming of the articles of commerce. The exact composition must, however, be known if the presence or absence of an ingredient (e.g., sucrose) is of therapeutic significance or when an additional ingredient must be incorporated in the product.

Elixirs contain ethyl alcohol. However, the alcoholic content will vary greatly, from elixirs containing only a small quantity, to those that contain a considerable portion as a necessary aid to solubility. For example, Aromatic Elixir USP contains 21 to 23% C_2H_5OH; Compound Benzaldehyde Elixir, on the other hand, contains 3 to 5% C_2H_5OH.

Elixirs may also contain glycerin and syrup. These may be added to increase the solubility of the medicinal agent or for sweetening purposes. Some elixirs contain propylene glycol. Claims have been made that this solvent is a satisfactory substitute for both glycerin and alcohol. Sumner,[8] in his paper on terpin hydrate preparations, summarized the advantages and disadvantages of this solvent and suggested several formulations with therapeutic characteristics superior to those of the elixir described in NF XIII.

One usual dose of the elixir (5 ml) contains 85 mg of terpin hydrate. This substance is used in bronchitis in doses of 125 to 300 mg as an expectorant. The elixir is, therefore, ineffective for the treatment of bronchitis. However, the elixir is used as a vehicle for the drugs in many commercially available cough syrups. These may contain dextromethorphan hydrobromide, codeine phosphate, chlorpheniramine maleate, pyrilamine maleate, ammonium chloride, creosote, chloroform, and a wide variety of other drugs with expectorant and antitussive properties.

Two of the four formulations described in Sumner's paper are given below:

Formulation 1

Terpin Hydrate	6.0 g
Lemon Tincture	5.0 ml
Orange Tincture	5.0 ml
Sodium Saccharin	0.5 g
Propylene Glycol	65.0 ml
Glycerin	15.0 ml
Sorbitol Solution, USP, a sufficient quantity, to make	100.0 ml

Dissolve the terpin hydrate in the propylene glycol and the glycerin which have been heated to 50°C. Dissolve the sodium saccharin in the tinctures and add to the solution of terpin hydrate at 25°C.

Add sufficient sorbitol solution to make the product measure 100 ml.

Formulation 2

Terpin Hydrate	6.0 g
Orange Oil	0.1 ml
Benzaldehyde	0.005 ml
Sorbitol Solution USP	10.0 ml
Propylene Glycol	40.0 ml
Alcohol	43.0 ml
Purified Water, a sufficient quantity, to make	100.0 ml

Dissolve the terpin hydrate in the propylene glycol and sorbitol solution which have been heated to 50°C. Add the oil and the benzaldehyde to the alcohol and mix with the terpin hydrate solution at 25°C. Add sufficient purified water to make the product measure 100 ml.

Both of these elixirs contain 300 mg of terpin hydrate/5 ml, a minimal quantity of alcohol, and flavoring agents which adequately mask the taste of propylene glycol.

Although alcohol is an excellent solvent for some drugs, it does accentuate the saline taste of bromides and similar salts. It is often desirable, therefore, to substitute some other solvent that is more effective in masking such tastes for part of the alcohol in the formula. In general, if taste is a consideration, the formulator is more prone to utilize a syrup rather than a hydroalcoholic vehicle.

An elixir may contain water and alcohol soluble ingredients. If such is the case, the following procedure is indicated:

Dissolve the water-soluble ingredients in part of the water. Add and solubilize the sucrose in the aqueous solution. Prepare an alcoholic solution containing the other ingredients. Add the aqueous phase to the alcoholic solution, filter, and make to volume with water.

Sucrose increases viscosity and decreases the solubilizing properties of water and so must be added after primary solution has been carried out. A high alcoholic content is maintained during preparation by adding the aqueous phase to the alcoholic solution. Elixirs should always be brilliantly clear. They may be strained or filtered and, if necessary, subjected to the clarifying action of purified talc or siliceous earth.

One of the official elixirs, Iso-Alcoholic Elixir (page 1241), is actually a combination of two solutions, one containing 8 to 10% ethanol and the other containing 73 to 78% ethanol. The elixir is used as a vehicle for various medicaments that require solvents of different alcohol strengths. For example, the alcohol strength of the elixir to be used with a single liquid galenical is approximately the same as that of the galenical. When different alcohol strengths are used in the same prescription, the elixir to be used is the one that produces the best solution. This is usually the average of the alcohol strengths of the several ingredients. For nonextractive substances, the lowest alcohol strength of elixir that will produce a clear solution should be used.

The formula for High-Alcoholic Elixir is:

Compound Orange Spirit	4 ml
Saccharin	3 g
Glycerin	200 ml
Alcohol, a sufficient quantity, to make	1000 ml

This elixir and many other liquid preparations intended for internal use (e.g., the diabetic syrups thickened with sodium carboxymethylcellulose or similar substances) contain saccharin. During the past few years, scientists have been studying the toxic effects of this sweetening agent and of the cyclamates. The cyclamate studies showed that the sweetener could produce cancer in animals and, as a result, this substance was removed from a wide variety of products. Similar studies have been carried out on saccharin.

Cyclamates and saccharin have been banned in some countries as ingredients in manufactured products. However, these substances may still be purchased as OTC products themselves. Much research has been done to find a safe synthetic substitute for sucrose.

Incompatibilities—Since elixirs contain alcohol, incompatibilities of this solvent are an important consideration during the formulation phase. Alcohol precipitates tragacanth, acacia, and agar from aqueous solutions. Similarly, it will precipitate many inorganic salts from similar solutions. The implication here is that such substances should be absent from the aqueous phase or should be present in such concentrations that there is no danger of precipitation on standing.

If an aqueous solution is added to an elixir, a partial precipitation of ingredients may occur. This is due to the reduced alcohol content of the final preparation. Usually, however, the alcohol content of the mixture is not sufficiently high to cause separation. As vehicles for tinctures and fluidextracts, the elixirs generally cause a separation of extractive matter from these products due to a reduction of the alcohol content.

Many of the incompatibilities between elixirs and the substances combined with them are due to the chemical characteristics of the elixir *per se* or of the ingredients in the final preparation. Thus certain elixirs are acid in reaction while others may be alkaline and will, therefore, behave accordingly.

A closely related group of preparations are the *cordials*. These are pleasantly flavored and are intended for internal administration. However, they are no longer official and, therefore, require no particular emphasis.

Glycerites

Glycerites are solutions or mixtures of medicinal substances in not less than 50% by weight of glycerin. Most of the glycerites are extremely viscous and some of them are of a jelly-like consistency. Few of the glycerites are extensively used.

Glycerin is a valuable pharmaceutical solvent forming permanent and concentrated solutions not otherwise obtainable. Some of these solutions are used in their original form as medicinal agents while others are used to prepare aqueous and alcoholic dilutions of substances which are not readily soluble in water or alcohol. One of the glycerites, Phenol Glycerin BPC is diluted with glycerin to form the pharmaceutical preparation, Phenol Ear-Drops BPC.

Phenol Glycerin BPC

Phenol	160 g
Glycerin	840 g

Dissolve the phenol in the glycerin.

Phenol Ear-Drops BPC

Phenol Glycerin	40 ml
Glycerin, a sufficient quantity, to make	100 ml

Add the glycerin to the glycerite.

Water should not be added to this preparation. It reacts with the phenol to produce a preparation which is caustic and, consequently, damaging to the area of application.

Although not within the context of the definitions given in this section, certain aqueous and nonaqueous preparations are used to remove wax (cerumen) from the ear. One commercially available preparation contains benzocaine, chlorbutol, *p*-dichlorobenzene, and turpentine; others contain olive oil, dioctyl sodium sulfosuccinate, or triethanolamine polypeptide oleate-condensate. Fraser[9] claims that the product first mentioned is superior to the other products tested but, in a review of this paper, it is suggested that the results of the study are contradictory and that Sodium Bicarbonate Ear-

Drops BPC should be used if wax is to be removed from the ear. This preparation contains sodium bicarbonate (5 g), glycerin (30 ml), and purified water (a sufficient quantity to make 100 ml). Although the product contains glycerin, it is not, by definition, a glycerite.

Starch Glycerite, an emollient, contains starch (100 g), benzoic acid (2 g), purified water (200 ml), and glycerin (700 ml).

Glycerites are hygroscopic and should be stored in tightly closed containers.

Inhalations and Inhalants

Inhalations

These preparations are so used or designed that the drug is carried into the respiratory tree of the patient. The vapor or mist reaches the affected area and gives prompt relief from the symptoms of bronchial and nasal congestion. The USP defines Inhalations in the following way:

Inhalations are drugs or solutions of drugs administered by the nasal or oral respiratory route for local or systemic effect. Examples in this Pharmacopeia are Epinephrine Inhalation and Isoproterenol Hydrochloride Inhalation. Nebulizers are suitable for the administration of inhalation solutions only if they give droplets sufficiently fine and uniform in size so that the mist reaches the bronchioles.

Another group of products, also known as inhalations and sometimes called insufflations, consists of finely powdered or liquid drugs that are carried into the respiratory passages by the use of special delivery systems such as pharmaceutical aerosols that hold a solution or suspension of the drug in a liquefied gas propellant (see Aerosols). When released through a suitable valve and oral adapter, a metered dose of the inhalation is propelled into the respiratory tract of the patient. Powders may also be administered by mechanical devices that require a manually produced pressure or a deep inspiration by the patient, e.g., *Cromolyn Sodium*.

Solutions may be nebulized by use of inert gases. Nebulized solutions may be breathed directly from the nebulizer, or the nebulizer may be attached to a plastic face mask, tent, or intermittent positive-pressure breathing (IPPB) machine.

A special class of inhalations termed "inhalants" consists of drugs or combinations of drugs that, by virtue of their high vapor pressure, can be carried by an air current into the nasal passage where they exert their effect. The container from which the inhalant is administered is known as an inhaler.

As stated in the pharmacopeia, particle size is of major importance in the administration of this type of preparation. The various types of mechanical devices that are used in conjunction with inhalations are described in some detail in Chapter 103. It has been reported in the literature that the optimum particle size for penetration into the pulmonary cavity is of the order of ½ to 7 μm. Fine mists are produced by pressurized aerosols and hence possess basic advantages over the older nebulizers. In addition to this, metered aerosols deliver more uniform doses than those obtained with the older mechanical devices. Chapter 92 should be consulted for further details on this subject.

The term *Inhalation* is used commonly by the layman to represent preparations intended to be vaporized with the aid of heat, usually steam, and inhaled. Benzoin Inhalation BPC contains benzoin, storax, and alcohol. The vapors from a preparation containing 1 teaspoonful of the tincture and 1 qt of boiling water may be inhaled. The device known as a *vaporizer* is used with a number of commercially available preparations of this type.

Epinephrine Inhalation and Isoproterenol Hydrochloride Inhalation are described in USP.

Inhalants

A companion preparation, the Inhalant, was described in NF XIV as follows:

Inhalants are drugs or combinations of drugs which, by virtue of their high vapor pressure, can be carried by an air current into the nasal passage where they exert their effect. The device making possible the administration of an inhalant is known as an *inhaler*. An example of such a product is *Propylhexedrine Inhalant*, which contains the volatile sympathomimetic, propylhexedrine.

Another group of products also known as inhalants or insufflations consists of finely powdered drugs or solutions of drugs that are carried into the respiratory passages by the use of special devices. Such devices include the low-pressure "aerosol" containers, which hold a solution or suspension of the drug in a liquefied propellant such as a fluorine or fluorine- and chlorine-substituted hydrocarbon. When released through a suitable spray nozzle, a metered dose of the inhalant is propelled into the respiratory tract of the patient. Powders may also be administered by other mechanical devices which require either manually produced air pressure, by means of an insufflator, or deep inspiration by the patient.

Propylhexedrine Inhalant and Tuaminoheptane Inhalant are described as consisting of cylindrical rolls of suitable fibrous material impregnated with propylhexedrine or tuaminoheptane (as carbonate), usually aromatized, and contained in a suitable inhaler. Propylhexedrine is the active ingredient in the widely used Benzedrex Inhaler.

Liniments

Liniments are solutions or mixtures of various substances in oil, alcoholic solutions of soap, or emulsions. They are intended for external application and should be so labeled. They are applied with rubbing to the affected area and, because of this, were once called *embrocations*. Dental liniments, which are no longer official, are solutions of active substances and are rubbed into the gums. Most dentists question their usefulness and, consequently, this type of preparation is relatively unimportant as a pharmaceutical form.

Liniments are usually applied with friction and rubbing of the skin, the oil or soap base providing for ease of application and massage. Alcoholic liniments are used generally for their rubefacient, counterirritant, mildly astringent, and penetrating effects. Such liniments penetrate the skin more readily than do those with an oil base. The oily liniments, therefore, are milder in their action but are more useful when massage is required. Depending on the ingredients in the preparation, such liniments may function solely as protective coatings. Liniments should not be applied to skin areas that are bruised or broken.

Many of the marketed "white" liniments are based on the formulation below or variations thereof.

White Liniment BPC

Ammonium Chloride	12.5 g
Dilute Ammonia Solution	45 ml
Oleic Acid	85 ml
Turpentine Oil	250 ml
Water	625 ml

Mix the oleic acid with the turpentine oil. Add the dilute ammonia solution mixed with 45 ml of previously warmed water. Shake. Dissolve the ammonium chloride in the remainder of the water, add to the emulsion, and mix.

Other liniments contain antipruritics, astringents, emollients, and analgesics and are classified on the basis of the active ingredient in the formulation. An example of a liniment in this category is:

Calamine Lotion, Oily BPC
(Calamine Liniment)

Calamine	50 g
Wool Fat	10 g
Oleic Acid	5 ml
Arachis Oil	500 ml
Calcium Hydroxide Solution	to 1000 ml

Triturate the calamine with the wool fat, the arachis oil, and the oleic acid, previously melted together. Transfer to a suitable container, add the calcium hydroxide solution, and shake vigorously.

Dermatologists prescribe products of this type but only those containing the rubefacients are extensively advertised

and used by consumers for treatment of minor muscular aches and pains.

Oleovitamins

Oleovitamins are fish liver oils diluted with edible vegetable oil or solutions of the indicated vitamins or vitamin concentrates (usually vitamins A and D) in fish liver oil. The definition is sufficiently broad to include a wide variety of marketed products.

Oleovitamin A and D is official. The vitamin D in the oleovitamin may be present as ergocalciferol or cholecalciferol obtained by the activation of ergosterol or 7-dehydrocholesterol or may be obtained from natural sources. Synthetic vitamin A or a concentrate may be used to prepare oleovitamin A. The starting material for the concentrate is a fish liver oil, the active ingredient being isolated by molecular distillation or by a saponification and extraction procedure. The latter procedure is described in detail in the monograph for Concentrated Vitamin A Solution BPC.

The indicated vitamins are unstable in the presence of rancid oils and, therefore, these preparations, and in particular, Oleovitamin A, should be stored in small, tight containers, preferably under vacuum or under an atmosphere of an inert gas, protected from light.

Spirits

Spirits, popularly known as essences, are alcoholic or hydroalcoholic solutions of volatile substances. Like the aromatic waters, the active ingredient in the spirit may be a solid, liquid, or gas. The genealogical tree for this class of preparations begins with the distinguished pair of products, Brandy (*Spiritus Vini Vitis*) and Whisky (*Spiritis Frumenti*), and ends with a wide variety of products that comply with the definition given above. Physicians have debated the therapeutic value of the former products and these are no longer official in the compendia.

Many of these spirits are used internally for their medicinal value, several are used medicinally by inhalation, while a large number are used as flavoring agents. The latter group provides a convenient and ready means of obtaining the volatile oil in the proper quantity. For example, a spirit or spirit-like preparation may be used in the formulation of aromatic waters or other pharmaceuticals that require a distinctive flavor.

Spirits should be stored in tight, light-resistant containers, and in a cool place. This prevents evaporation and volatilization of either the alcohol or the active principle.

Preparation—There are four classic methods for the preparation of this official group: These are *simple solution, solution with maceration, chemical reaction,* and *distillation.*

Simple Solution—This is the method by which the majority of spirits are prepared. The formula and procedure given for Aromatic Ammonia Spirit illustrate this method of preparation.

Aromatic Ammonia Spirit

Ammonium Carbonate, in translucent pieces	34 g
Strong Ammonia Solution	36 ml
Lemon Oil	10 ml
Lavender Oil	1 ml
Nutmeg Oil	1 ml
Alcohol	700 ml
Purified Water, a sufficient quantity to make	1000 ml

Dissolve the ammonium carbonate in the strong ammonia solution and 195 ml of purified water by gentle agitation, and allow the solution to stand for 12 hours. Dissolve the oils in the alcohol, contained in a graduated bottle or cylinder, and gradually add the ammonium carbonate solution and enough purified water to make the product measure 1000 ml. Set the mixture aside in a cool place for 24 hours, occasionally agitating it, and then filter, using a covered funnel.

The spirit is a respiratory stimulant and is administered by inhalation of the vapor as required. It is marketed in suitable tight, light-resistant containers but is also available in a single-dose glass vial wrapped in a soft cotton envelope. The vial is easily broken; the cotton acts as a sponge for the spirit.

Ammonium carbonate is a mixture of ammonium bicarbonate and ammonium carbamate (NH_2COONH_4). The carbamate reacts with water to form the carbonate.

$$NH_2COONH_4 + H_2O \rightarrow (NH_4)_2CO_3$$

An ammonium carbonate solution is, therefore, a solution of ammonium bicarbonate and ammonium carbonate in water. However, it decomposes in water, the decomposition products being ammonia, carbon dioxide, and water. The stability of the spirit is improved by the addition of strong ammonia solution. This represses the hydrolysis of ammonium carbonate and, in this way, decreases the loss of dissolved gases.

Solution with Maceration—In this procedure, leaves of the drug are macerated in purified water to extract water-soluble matter. They are then expressed, and the moist macerated leaves are added to a prescribed quantity of alcohol. The volatile oil is added to the filtered liquid. Peppermint Spirit is made by this process. Peppermint Spirit BPC differs from the official product in that it is a solution of the volatile oil in alcohol only. The concentration of volatile oil in the final product is about the same but the official preparation possesses a green color. The ready availability of soluble chlorophyll and other coloring agents has led to the frequent suggestion that a more uniform product could be obtained through their use. However, these agents cannot be used in preparing the official article.

The formula and procedure for Peppermint Spirit (page 756) illustrate this method of preparation.

Chemical Reaction—No official spirits are prepared by this process. Ethyl nitrite is made by the action of sodium nitrite on a mixture of alcohol and sulfuric acid in the cold. This substance is then used to prepare Ethyl Nitrite Spirit, a product no longer official.

Distillation—Brandy and Whisky are made by distillation. The latter is derived from the fermented mash of wholly or partially germinated malted cereal grains and the former from the fermented juice of ripe grapes.

Incompatibilities—Spirits are, for the most part, preparations of high alcoholic strength and do not lend themselves well to dilution with aqueous solutions or liquids of low alcoholic content. The addition of such a solution invariably causes separation of some of the material dissolved in the spirit, evidenced by a turbidity which, in time, may disappear as distinct layering occurs. Salts may be precipitated from their aqueous solutions by addition of spirits due to lesser solubility in alcoholic liquids.

Some spirits show incompatibilities characteristic of the ingredients which they contain. For example, Aromatic Ammonia Spirit cannot be mixed with aqueous preparations containing alkaloids (e.g., codeine phosphate). An acid-base reaction (ammonia-phosphate) occurs and, if the alcohol content of the final mixture is too low, codeine will precipitate.

Toothache Drops

Toothache drops are preparations used for temporary relief of toothache by application of a small pledget of cotton saturated with the product into the tooth cavity. Clove oil and

mixtures of phenol with camphor or creosote are probably the most frequently used toothache remedies. When phenol, creosote, or volatile oils are dissolved in paraffin to which a few filaments of cotton have been added, and the mixture molded into sticks, a preparation referred to as *dental wax* is formed.

These preparations are no longer officially recognized. Furthermore, dentists do not recommend use of toothache drops if the patient has ready access to adequate dental services. The preparations may damage the gums and produce complications more severe than the original toothache. However, many areas do not have adequate dental services and the pharmacist will, of necessity, handle these preparations. If such is the case, the pharmacist should warn the patient of possible hazards associated with the use of these products.

Toothache Drops NF XI contain 25 g of chlorobutanol in sufficient clove oil to make the product measure 100 ml. Another formulation contains creosote, clove oil, benzocaine, and alcohol in a flexible collodion base.

Emulsions

An emulsion is a two-phase system prepared by combining two immiscible liquids, one of which is uniformly dispersed throughout the other and consists of globules that have diameters equal to or greater than those of the largest colloidal particles. The globule size is, of course, critical and must be such that the system achieves maximum stability. However, even under the best of conditions, separation of the two phases will occur unless a third substance, an *emulsifying agent,* is incorporated. The basic emulsion must, therefore, contain three components but the products of commerce may consist of a number of therapeutic agents dissolved in either of the two phases of the preparation.

Most emulsions are so prepared as to incorporate an aqueous phase into a nonaqueous phase (or *vice versa*). However, it is possible to prepare emulsions that are basically nonaqueous. For example, investigations of the emulsifying effects of anionic and cationic surfactants on the nonaqueous immiscible system, glycerin and olive oil, have shown that certain amines and three cationic agents produced stable emulsions. This broadening of the basic definition for the term *emulsion* is recognized in the USP.

An emulsion is a two-phase system in which one liquid is dispersed in the form of small droplets throughout another liquid. The dispersed liquid is known as the internal or discontinuous phase, whereas the dispersion medium is known as the external or continuous phase. Where oil is the dispersed phase and an aqueous solution is the continuous phase, the system is designated as an oil-in-water (O/W) emulsion and this can be easily and uniformly diluted with water. Conversely, where water or an aqueous solution is the dispersed phase and oil or oleaginous material is the continuous phase, the system is designated as a water-in-oil (W/O) emulsion.

Many emulsifying agents are available for use in preparing emulsions, among them the following:

Natural Emulsifying Agents—These substances may be derived from either animal or vegetable sources. Examples of those obtained from the former source are gelatin, egg yolk, casein, wool fat, and cholesterol. Acacia, tragacanth, chondrus, and pectin are representative of those obtained from vegetable sources. Various cellulose derivatives, e.g., methylcellulose and carboxymethylcellulose, are used to increase viscosity of the aqueous phase and thereby enhance emulsion stability.

Finely Divided Solids—Examples of emulsifying agents of this type are bentonite, magnesium hydroxide, aluminum hydroxide, and magnesium trisilicate.

Synthetic Emulsifying Agents—This group may be further subdivided into the anionic, cationic, and nonionic agents. Examples of these three types of emulsifying agents are, in order of presentation, sodium lauryl sulfate, benzalkonium chloride, and polyethylene glycol 400 monostearate.

Many of these emulsifying agents are described in greater detail in Chapter 67.

NF XIII suggested that only O/W emulsions are suitable for oral use because these are water-miscible and thus their oiliness is masked. This compendium gave specific directions for the preparation of emulsions utilizing gelatin as an emulsifying agent. These preparations are based on either type A or type B gelatin. Type A gelatin is prepared from acid-treated precursors and is used at a pH of about 3.2. It is incompatible with anionic emulsifying agents such as the vegetable gums. The following formula was recommended:

Gelatin (Type A)	8 g
Tartaric Acid	0.6 g
Flavor as desired	
Alcohol	60 ml
Oil	500 ml
Purified Water, to make	1000 ml

Add the gelatin and the tartaric acid to about 300 ml of purified water, allow to stand for a few minutes, heat until the gelatin is dissolved, then raise the temperature to about 98°, and maintain this temperature for about 20 min. Cool to 50°, and add the flavor, the alcohol, and sufficient purified water to make 500 ml. Add the oil, agitate the mixture thoroughly, and pass it through a homogenizer or a colloid mill until the oil is completely and uniformly dispersed.

This emulsion cannot be prepared by trituration or by the use of the usual stirring devices.

Type B gelatin is prepared from alkali-treated precursors and is used at a pH of about 8.0. It may be used with other anionic emulsifying agents but is incompatible with cationic types. If the emulsion contains 50% oil, 5 g of Type B gelatin, 2.5 g of sodium bicarbonate, and sufficient tragacanth or agar should be incorporated into the aqueous phase so as to yield 1000 ml of product of the required viscosity.

The emulsion type (O/W or W/O) is of lesser significance if the final preparation is to be applied to the skin. If there are no breaks in the skin, a W/O emulsion can be applied more evenly since the skin is covered with a thin film of sebum. The latter substance favors the oily phase and contributes to the ease of application. The choice of emulsion type will, however, depend on many other factors. This is particularly true for those preparations which have basic cosmetic characteristics. It may be advantageous to formulate an O/W emulsion if ease of removal is an important consideration to the patient.

An emulsion that may be prepared by the mortar and pestle method is the following Mineral Oil Emulsion.

Mineral Oil	500 ml
Acacia, very fine powder	125 g
Syrup	100 ml
Vanillin	40 mg
Alcohol	60 ml
Purified Water, to make	1000 ml

The mineral oil and acacia are mixed in a dry Wedgwood mortar. Water (250 ml) is added and the mixture is triturated vigorously until an emulsion is formed. A mixture of the syrup, 50 ml of purified water and the vanillin dissolved in alcohol is added in divided portions with trituration; sufficient purified water is then added to the proper volume. The mixture is mixed well and homogenized.

Very few emulsions are now included in the official compendia. The BPC states that the term "emulsion" should be restricted to oil-in-water preparations intended for internal use and lists the following: Liquid Paraffin Emulsion, Liquid Paraffin and Magnesium Hydroxide Emulsion, Liquid Par-

affin and Phenolphthalein Emulsion, Liquid Paraffin Emulsion with Cascara, and Concentrated Peppermint Emulsion.

This, however, should not lead the student to the conclusion that emulsions are a relatively unimportant class of pharmaceuticals. While it is true that few preparations carry the term *emulsion* in their titles, they are of great significance as bases for other types of preparations, particularly in the dermatological and cosmetic areas. Academically, they illustrate the importance of the relationship between the theory and practice of emulsion technology and, practically, they possess a number of important advantages over other liquid forms. These may be summarized in the following way:

1. In an emulsion, the therapeutic properties and the spreading ability of the constituents are increased.
2. The unpleasant taste or odor of the oil can be partially or wholly masked by the process of emulsification. Secondary masking techniques are available to the formulator but these must be used with caution. If flavors and sweetening agents are added to the emulsion, only minimal amounts should be used in order to prevent the nausea or gastric distress that results on ingestion of larger quantities of these formulation aids.
3. The absorption and penetration of medicaments are more easily controlled if they are incorporated into an emulsion.
4. Emulsion action is more prolonged and the emollient effect is greater than that observed with comparable preparations.
5. Water is not only an inexpensive diluent but is a good solvent for the many drugs and flavors that are incorporated into the emulsion.

The aqueous phase of the emulsion favors the growth of microorganisms and, because of this, a preservative is usually added to the product. Some of the preservatives that have been used in emulsions include chlorocresol, chlorobutanol, mercurial preparations, salicylic acid, the esters of *p*-hydroxybenzoic acid, benzoic acid, sodium benzoate, and sorbic acid. The preservative should be selected having regard for the use of the preparation and possible incompatibilities between the preservative and the ingredients in the emulsion, e.g., binding between the surface-active agent and the preservative.

Most emulsions consist of an oil phase and a water phase, thus some of the preservative may pass into the oil phase and be removed from the aqueous phase. It is in the aqueous phase that microorganisms tend to grow. As a result, water-soluble preservatives are more effective since the concentration of the unbound preservative in the water phase assumes a great deal of importance in inhibiting the microbial growth. Esters of *p*-hydroxybenzoic acid appear to be the most satisfactory preservatives for emulsions. Many mathematical models have been used in determining availability of preservatives in emulsified systems. However, because of the number of factors which reduce the effectiveness of the preservative, a final microbiological evaluation of the emulsion should be performed.

While emphasis concerning preservation of emulsions deals with the aqueous phase, microorganisms can reside also in the lipid (oil) phase. Consequently, it has been recommended that pairs of preservatives be used to ensure adequate concentration in both phases.[10] Esters of *p*-hydroxybenzoic acid can be used to ensure appropriate concentrations in both phases because of their difference in oil and water solubilities.

An emulsion can be diluted with the liquid that constitutes or is miscible with the external phase. The diluting liquid will, however, decrease the viscosity of the preparation and, in certain instances, will invert the emulsion. The latter phenomena may occur if the emulsifier-in-water method (see below) is used to prepare the emulsion.

Preparation

The theory of emulsion preparation is discussed in Chapter 21. The following procedures are those suggested by Griffin *et al.*[11]

The formulator must first determine the physical and chemical characteristics of the active ingredient. He must know the following:

1. Structural formula
2. Melting point
3. Solubility
4. Stability
5. Dose
6. Specific chemical incompatibilities

It is also necessary, at this stage, to decide on the type of emulsion required. Washable emulsions are of the O/W type; nonwashable, the W/O type. In general, O/W emulsions contain over 70% water. W/O emulsions will usually contain higher concentrations of oils and waxes.

Experimental formulations may be prepared by the following procedure:

1. Group the ingredients on the basis of their solubilities in the aqueous and nonaqueous phases.
2. Determine the type of emulsion required and calculate an approximate HLB value.
3. Blend a low HLB emulsifier and a high HLB emulsifer to the calculated value. For experimental formulations, use a higher concentration of emulsifier (e.g., 10–30% of the oil phase) than that required to produce a satisfactory product. Emulsifiers should, in general, be chemically stable, nontoxic, and suitably low in color, odor, and taste. The emulsifier is selected on the basis of these characteristics, on the type of equipment being used to blend the ingredients, and on the stability characteristics of the final product. Emulsions should not coalesce at room temperature, when frozen and thawed repeatedly, and at elevated temperatures of up to 50°C. Mechanical energy input varies with the type of equipment used to prepare the emulsion. The more the energy input, the less the demand on the emulsifier. Both process and formulation variables can affect the stability of an emulsion.
4. Dissolve the oil-soluble ingredients and the emulsifiers in the oil. Heat, if necessary, to approximately 5° to 10°C over the melting point of the highest melting ingredient or to a maximum temperature of 70° to 80°C.
5. Dissolve the water-soluble ingredients (except acids and salts) in a sufficient quantity of water.
6. Heat the aqueous phase to a temperature which is 3° to 5°C higher than that of the oil phase.
7. Add the aqueous phase to the oily phase with suitable agitation.
8. If acids or salts are employed, dissolve them in water and add the solution to the cold emulsion.
9. Examine the emulsion and make adjustments in the formulation if the product is unstable. It may be necessary to add more emulsifier, to change to an emulsifier with a slightly higher or lower HLB value, or to use an emulsifier with different chemical characteristics.

Becher[12] described four methods of preparation based on the mode of addition of the ingredients.

Emulsifier-in-Water Method—The emulsifying agent is dissolved in the water and the oil is added, with agitation, to the aqueous solution. An O/W emulsion is produced but inversion (to a W/O emulsion) will take place if more oil is added to the preparation.

Emulsifier-in-Oil Method—The emulsifier is dissolved in oil. The mixture may be added directly to the water to form an O/W emulsion or water may be added to the mixture to form a W/O emulsion. The Emulsifier-in-Oil Method is the *Continental Method* for the preparation of emulsions.

Soap Method—This method may be used to prepare emulsions stabilized by soaps. The fatty acid part of the "soap" is dissolved in the oil; the alkaline part, in the water. Soap forms at the interface when the two phases are brought together. This method may be used to prepare either O/W or W/O emulsions.

Alternate Addition Method—The emulsion is prepared by adding water and oil alternately to the emulsifying agent. This is the so-called *English Method* for the preparation of emulsions. The emulsifying agent (e.g., acacia) is first triturated with twice its weight of water. Small quantities of oil are now added to the mucilage. The mixture is triturated for several minutes and, if it becomes too viscous, a small quantity of water is added to the primary emulsion. The remaining oil, active ingredients, and water are then incorporated into the preparation.

Equipment

When emulsions are prepared, energy must be expended to form an interface between the oily and aqueous phases. Emulsification equipment includes, therefore, a wide variety of agitators, homogenizers, colloid mills, and ultrasonic de-

vices. Griffin, *et al*,[11] Becher,[12] and Peck, *et al*,[13] have evaluated the emulsification equipment used by pharmacists and drug manufacturers. These publications should be consulted for further details on the use of such apparatus for the preparation of emulsions and related products.

Agitators—Ordinary agitation or shaking may be used to prepare the emulsion. This method is frequently employed by the pharmacist, particularly in the emulsification of easily dispersed, low-viscosity oils. Under certain conditions, intermittent shaking is considerably more effective than ordinary continuous shaking. Continuous shaking tends to break up not only the phase to be dispersed but also the dispersion medium and, in this way, impairs ease of emulsification. Laboratory shaking devices may be used for small-scale production of emulsions. However, Clayton[14] claims that shaking is an inferior method for production of emulsions "because, as the emulsion becomes more perfect, the smashing action between the relatively heavy and light particles becomes more feeble, whereas the smashing forces should be increased."

The mortar and pestle are widely used by the prescription pharmacist in extemporaneous preparation of emulsions. This equipment has very definite limitations because its usefulness depends largely on the viscidity of the emulsifying agent. A mortar and pestle cannot be used to prepare an emulsion if the emulsifying agent lacks viscidity (e.g., gelatin solutions). These emulsifying agents will produce stable emulsions only if other types of equipment are used to mix the ingredients and the agent together.

Small electric mixers may be used to prepare emulsions at the prescription counter. These mixers will save time and energy and produce satisfactory emulsions when the emulsifying agent is acacia or agar. However, the mixers cannot be used if the emulsifying agent is gelatin.

The commercially available *Waring Blendor* disperses efficiently by means of the shearing action of rapidly rotating blades. This mixer transfers large amounts of energy and incorporates air into the emulsion. If an emulsion is first produced by using a blender of this type, the formulator must remember that the emulsion characteristics obtained in the laboratory will not necessarily be duplicated by the production-size agitators.

Production-size agitators include high-powered propeller shaft stirrers immersed in a tank or self-contained units with propeller and paddle systems. The latter units are usually so constructed that the contents of the tank may be either heated or cooled during the production process. Baffles are often built into a tank and these increase the efficiency of agitation. Two mixers manufactured by the same company are shown in Figs. 83-2 and 83-3.

Colloid Mills—The principle of operation of the colloid mill is the passage of the mixed phases of an emulsion formula between a stator and a high-speed rotor revolving at speeds of 2000–18,000 rpm. The clearance between the rotor and the stator is adjustable, usually from 0.001 in. upward. The emulsion mixture, in passing between the rotor and stator, is subjected to a tremendous shearing action which effects a fine dispersion. Two of the many types of colloid mills on the market are shown in Figs. 83-4 to 83-6. The operating principle is the same for all but each manufacturer incorporates specific features which result in changes in operating efficiency. The shearing forces applied in the colloid mill may result in a temperature increase within the emulsion. It may be necessary, therefore, to cool the equipment when the emulsion is being produced.

Homogenizers and Viscolizers—In the viscolizer and the homogenizer, the mixed phases are passed between a finely ground valve and seat under high pressure. This, in effect, produces an atomization which is enhanced by the impact received by the atomized mixture as it strikes the valve head.

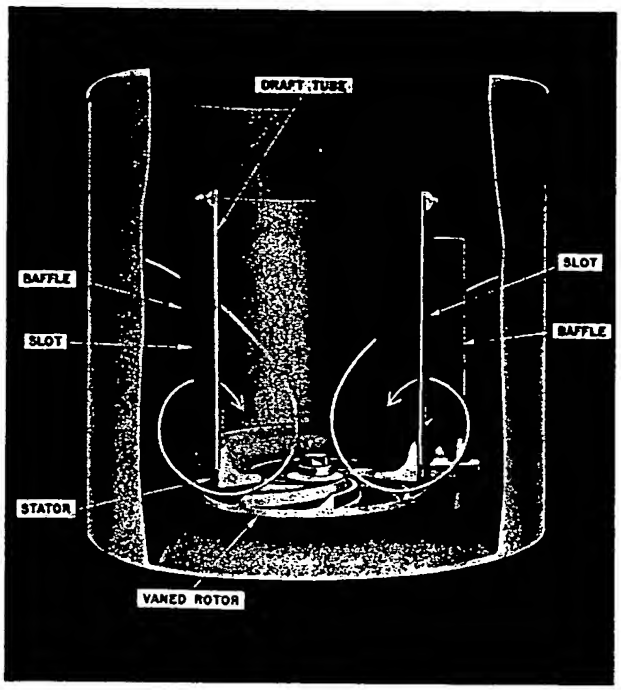


Fig. 83-2. Standard slurry-type dispersall mixer with vaned-rotor "mixing" element and slotted draft-tube circulating element (courtesy, Abbe Eng.).

This type of apparatus operates at pressures of 1000–5000 lb/sq in. and produces some of the finest dispersions obtainable in an emulsion.

Homogenizers may be used in one of two ways: (1) the ingredients in the emulsion are mixed and then passed through the homogenizer to produce the final product; or (2) an emulsion is prepared in some other way and is then passed

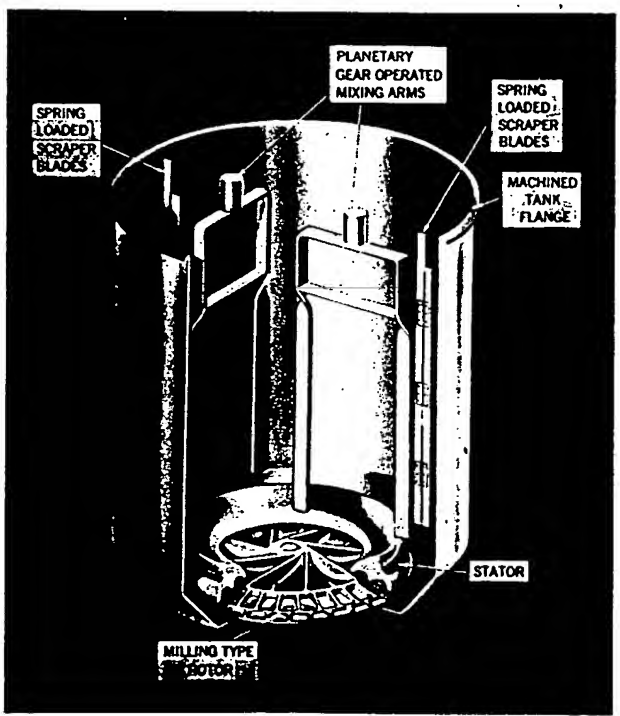


Fig. 83-3. Standard paste-type dispersall mixer with "cupped-rotor" milling element and double-rotating mixing arm circulating element (courtesy, Abbe Eng.).

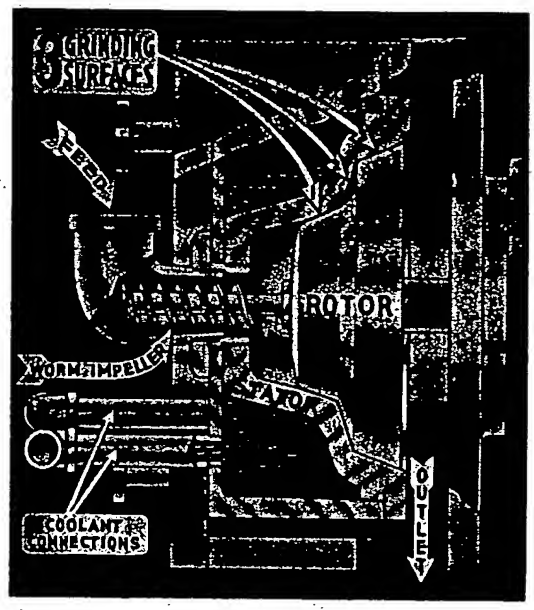


Fig. 83-4. A colloid mill shown in cross section (courtesy, Tri-Homo).

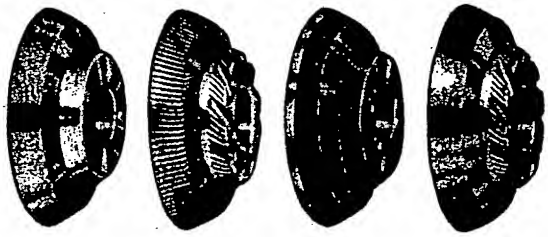


Fig. 83-5. Types of rotors used in colloid mills. These may be smooth (for emulsification of most emulsions), serrated (for the emulsification of ointments and very viscous products), or of vitrified stone (for the emulsifications of paints and pigment dispersions) (courtesy, Tri-Homo).

through a homogenizer for the purpose of decreasing the particle size and obtaining a greater degree of uniformity and stability.

Two-stage homogenizers (Fig. 83-7) are so constructed that the emulsion, after treatment in the first valve system, is conducted directly to another where it receives a second treatment. A single homogenization may produce an emulsion which, although its particle size is small, has a tendency to clump or form clusters. Emulsions of this type exhibit increased creaming tendencies. This is corrected by passing the emulsion through the first stage of homogenization at a high pressure (e.g., 3000–5000 lb/sq in.) and then through the second stage at a greatly reduced pressure (e.g., 1000 lb/sq in.). This breaks down any clusters formed in the first step.

Fig. 83-6. The Premier colloid mill, a gravity flow, vertical colloid mill with only one moving member, the rotor. Adjustment of clearance between the rotor and stator can be made from 0.001 in. upward. Speeds range from 3600 to 17,600 rpm for this type of mill, which may be used for the even and uniform distribution of the ingredients in a wide range of pharmaceutical products.

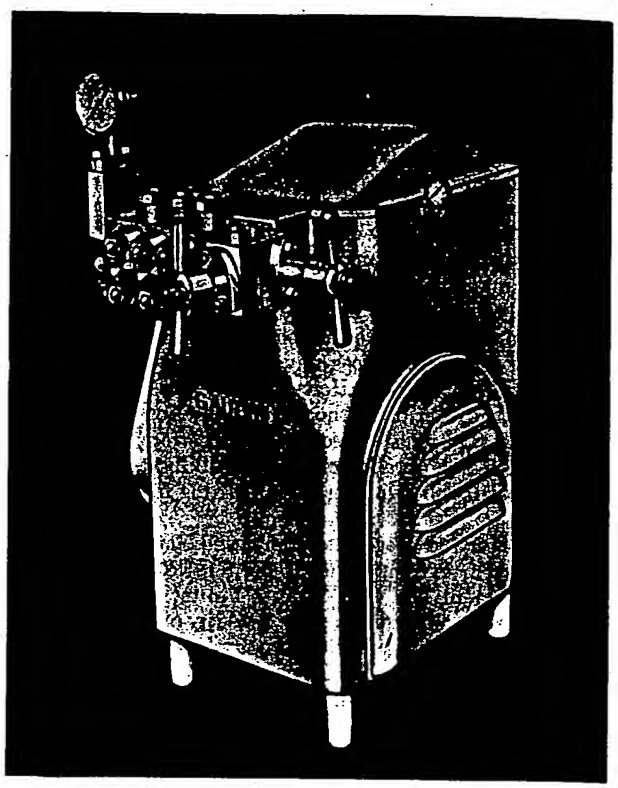


Fig. 83-7. Two-stage homogenizer (courtesy, Manton Gaulin).

For small-scale extemporaneous preparation of emulsions, the inexpensive *hand homogenizer* (available from *Med. Times*) is particularly useful. It is probably the most efficient emulsifying apparatus available to the prescription pharmacist. The two phases, previously mixed in a bottle, are hand pumped through the apparatus. Recirculation of the emulsion through the apparatus will improve its quality.

A homogenizer does not incorporate air into the final product. Air may ruin an emulsion because the emulsifying agent is preferentially adsorbed at the air/water interface. This is followed by an irreversible precipitation termed *denaturization.* This is particularly prone to occur with protein emulsifying agents.

Homogenization may spoil an emulsion if the concentration of emulsifying agent in the formulation is less than that required to take care of the increase in surface area produced by the process.

The temperature rise during homogenization is not very large. However, temperature does play an important role in the emulsification process. An increase in temperature will reduce the viscosity and, in certain instances, the interfacial tension between the oil and the water. There are, however, many instances, particularly in the manufacturing of cosmetic creams and ointments, where the ingredients will fail to emulsify properly if they are processed at too high a temperature. Emulsions of this type are first processed at an elevated temperature and then homogenized at a temperature not exceeding 40°C.

The Marco Flow-Master Kom-bi-nator (Fig. 83-8) employs a number of different actions, each of which takes the ingredients a little further along in the process of subdividing droplets until complete homogenization results. The machine is equipped with a pump which carries the liquid through the various stages of the process. In the first stage, the ingredients are forced between two specially designed rotors (gears)

which shoot the liquid in opposite directions in a small chamber and, in this way, mixed thoroughly. These rotors also set up a swirling action in the next chamber into which the liquid is forced and swirled back and forth in eddies and cross currents. The second stage is a pulsing or vibrating action at rapid frequency. The product then leaves this chamber, goes through a small valve opening, and is dashed against the wall of the homogenizing chamber. Pressure is applied but is not as great as that used in other types of homogenizers. Pressure is accurately controlled by adjusting devices on the front of the machine, and temperature is controlled by passing coolants through the stators.

Ultrasonic Devices—The preparation of emulsions by the use of ultrasonic vibrations is also possible. An oscillator of high frequency (100,000–500,000/sec) is connected to two electrodes between which is placed a piezoelectric quartz plate. The quartz plate and electrodes are immersed in an oil bath and, when the oscillator is operating, high-frequency waves flow through the fluid. Emulsification is accomplished by simply immersing a tube containing the emulsion ingredients into this oil bath. Considerable research has been done on ultrasonic emulsification, particularly with regard to the mechanism of emulsion formation by this method. Limited data indicate that these devices will produce stable emulsions only with liquids of low viscosity. The method is not, however, practical for large-scale production of emulsions.

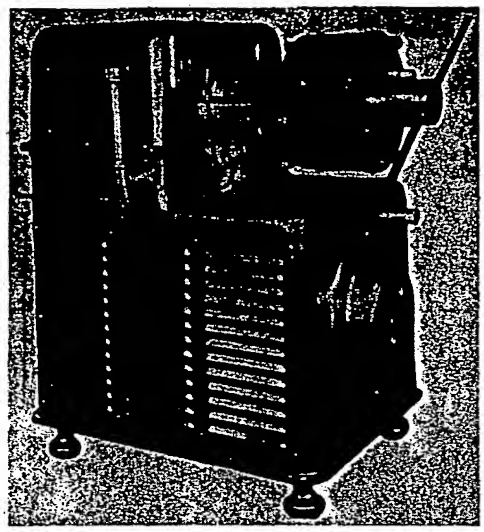


Fig. 83-8. Marco Flow-Master Kom-bi-nator combines the functions of a homogenizer and a colloid mill (courtesy, Marco).

Special techniques and equipment will, in certain instances, produce superior emulsions, including rapid cooling, reduction in particle size, ultrasonic devices, etc.

Suspensions

The physical chemist defines the word "suspension" as a two-phase system consisting of a finely divided solid dispersed in a solid, liquid, or gas. The pharmacist accepts this definition and can show that a variety of dosage forms fall within the scope of the preceding statement. There is, however, a reluctance to be all-inclusive and it is for this reason that the main emphasis is placed on solids dispersed in liquids. In addition to this, and because there is a need for more specific terminology, the pharmaceutical scientist differentiates between such preparations as Suspensions, Mixtures, Magmas, Gels, and Lotions. In a general sense, each of these preparations represents a suspension but the state of subdivision of the insoluble solid varies from particles which gradually subside on standing to particles which are colloidal in nature. The lower limit of particle size is approximately 0.1 micrometer and it is the preparations containing dispersed solids of this magnitude or greater that are pharmaceutically defined as suspensions.

Certain authors also include liniments and the newer sustained-release suspensions in any discussion of this particular subject. The former preparations are now usually considered as solutions although a number of older liniments were, in fact, suspensions. The sustained-release suspensions represent a very specialized class of preparation, and as such, are discussed in more detail in Chapter 91. Some insoluble drugs are also administered in aerosol form. One example of such a preparation is dexamethasone phosphate suspended in a propellant mixture of fluorochlorocarbons. More detail on aerosols is available in Chapter 92.

Suspension formulation and control is based on the principles outlined in Chapters 19 to 22. Formulation involves more than suspending a solid in a liquid. A knowledge of the behavior of particles in liquids, of suspending agents, and of flavors and colors is required to produce a satisfactory suspension. Chong[15] lists the following procedure for formulating suspensions.

1. Determine the ionic character of the drug.
2. Determine the ionic character of each of the other ingredients in the formula. If possible, use nonionic ingredients.
3. Determine the density of the drug and the size of the largest particle to be suspended. At this point, select the most suitable suspending agent.
4. After incorporating the suspending agent and the bulk ingredients, determine the density of the suspension medium.
5. Determine the sedimentation force of the particles.
6. Determine the concentration of the suspending agent.
7. Formulate the suspension medium and check its rheological behavior before adding the powdered drug.

Preparations such as those mentioned above possess certain advantages over other dosage forms. Some drugs are insoluble in all acceptable media and must, therefore, be administered as a tablet, capsule, etc., or as a suspension. Because of its liquid character, the last preparation insures some uniformity of dosage but does present some problems in maintenance of a consistent dosage regimen. Disagreeable tastes can be covered by use of a suspension of the drug or a derivative of the drug, an example of the latter being the drug chloramphenicol palmitate. Suspensions are also chemically more stable than solutions. This is particularly important with certain antibiotics and the pharmacist is often called on to prepare such a suspension just prior to the dispensing of the preparation. In addition to this, a suspension is an ideal dosage form for patients who have difficulty swallowing tablets or capsules. This factor is of particular importance in administration of drugs to children.

Suspensions should possess certain basic properties. The dispersed phase should settle slowly and should be readily redispersed on shaking. They should not cake on settling and the viscosity should be such that the preparation pours easily. As with all dosage forms, there should be no question as to the chemical stability of the suspension. Lastly, the suspension must be acceptable to the patient on the basis of its taste, color, and cosmetic qualities, the latter two factors being of particular importance in preparations intended for external use.

Calamine Lotion

Calamine	8 g
Zinc Oxide	8 g
Glycerin	2 ml
Avicel R Gel	2 g
Carboxymethylcellulose	2 g
Calcium Hydroxide Solution, a sufficient quantity, to make	100 ml

Phenolated Calamine Lotion

Calamine	8 g
Zinc Oxide	8 g
Glycerin	2 ml
Avicel R Gel	2 g
Carboxymethylcellulose	2 g
Liquefied Phenol	1 ml
Calcium Hydroxide Solution, a sufficient quantity, to make	100 ml

Mix 45 g of Avicel R with 55 g of water in a suitable electric mixer. This gel is used in the preparation of the calamine lotion. Mix the calamine and the zinc oxide with the glycerin, the gel and the carboxymethylcellulose. Add sufficient calcium hydroxide solution to make the product measure 100 ml.

Suspensions may also be formed by chemical interaction in the liquid. White Lotion is an example of this type of preparation.

White Lotion

Zinc Sulfate	40 g
Sulfurated Potash	40 g
Purified Water, a sufficient quantity to make	1000 ml

Dissolve the zinc sulfate and the sulfurated potash separately, each in 450 ml of purified water, and filter each solution. Add slowly the sulfurated potash solution to the zinc sulfate solution with constant stirring. Then add the required amount of purified water, and mix.

Sulfurated potash is a solid of variable composition but is usually described as $K_2S_3 \cdot K_2S_2O_3$. The chemical reaction which occurs when sulfurated potash solution is added to the zinc sulfate solution is given below.

$$ZnSO_4 \cdot 7H_2O + K_2S_3 \cdot K_2S_2O_3 \rightarrow ZnS\downarrow + S_2\downarrow + K_2SO_4 + K_2S_2O_3 + 7H_2O$$

This lotion must be freshly prepared and does not contain a suspending agent. Bentonite Magma has been used in some formulations. Coffman and Huyck[16] include a detailed discussion of the chemistry and the problems involved in the preparation of a suitable product.

The USP recognizes a second type of lotion. These are emulsions of the O/W type stabilized by a surface-active agent. Benzyl Benzoate Lotion is an example of this type of preparation. Lastly, some lotions are clear solutions and, in fact, the active ingredient of one official lotion, Dimethisoquin Hydrochloride Lotion, is a water-soluble substance. However, one unofficial formulation for this lotion lists dimethisoquin hydrochloride, menthol, and zinc oxide as active ingredients and the preparation thus becomes a suspension.

Lotions are usually applied without friction. Even so, the insoluble matter should be very finely divided. Particles approaching colloidal dimensions are more soothing to inflamed areas and are more effective in contact with infected surfaces. A wide variety of ingredients may be added to the preparation to produce better dispersions or to accentuate the cooling, soothing, drying, or protective properties of the lotion. Bentonite is a good example of a suspending agent used in the preparation of lotions. Methylcellulose or sodium carboxymethylcellulose will localize and hold the active ingredient in contact with the affected site. A formulation containing glycerin will keep the skin moist for a considerable period of time. The drying and cooling effect may be accentuated by the addition of alcohol to the formula.

Dermatologists frequently prescribe lotions containing anesthetics, antiseptics, astringents, germicides, protectives, or screening agents, to be used in treating or preventing various types of skin diseases and dermatitis. Antihistamines, benzocaine, calamine, resorcin, steroids, sulfur, zinc oxide, and zirconium oxide are common ingredients in unofficial lotions. In many instances the cosmetic aspects of the lotion are of great importance. Many lotions compare badly with cosmetic preparations of a similar nature. The manufacture of fine lotions to meet the specialized needs of the dermatologist provides the pharmacist with an excellent opportunity to demonstrate his professional competence. Recent extensive studies on lotions will assist the pharmacist to gain this goal.[17]

Lotions tend to separate or stratify on long standing, and they require a label directing that they be shaken well before each use. All lotions should be labeled "For External Use Only."

Microorganisms may grow in certain lotions if no preservative is included in the preparation. Care should be taken to avoid contaminating the lotion during preparation, even if a preservative is present.

Magmas and Milks

Magmas and milks are aqueous suspensions of insoluble, inorganic drugs and differ from gels mainly in that the suspended particles are larger. When prepared, they are thick and viscous, and because of this, there is no need to add a suspending agent to the preparation.

Bentonite Magma USP (page 1244) is prepared by simple hydration. Two procedures are given in the compendium for the preparation of this product.

Magmas may also be prepared by chemical reaction. Magnesium hydroxide is prepared by the hydration of magnesium oxide.

$$MgO + H_2O \rightarrow Mg(OH)_2$$

Milk of Magnesia USP (page 738) is a suspension of magnesium hydroxide containing 7.0–8.5% $Mg(OH)_2$. It has an unpleasant alkaline taste. This taste can be masked with 0.1% citric acid and 0.05% of a volatile oil or a blend of volatile oils. The citric acid reduces the alkalinity of the preparation.

Milk of Bismuth (page 736) contains bismuth hydroxide and basic bismuth carbonate in suspension in water. The Magma is prepared by reacting bismuth subnitrate with nitric acid and ammonium carbonate with ammonia solution and then mixing the resulting two solutions.

The following reactions occur during the preparation of the magma.

$$(NH_4)_2CO_3 \rightarrow 2NH_4^+ + CO_3^=$$

$$NH_3 + H_2O \rightarrow NH_4^+ + OH^-$$

$$2BiO^+ + CO_3^= \rightarrow (BiO)_2CO_3\downarrow$$

$$BiO^+ + OH^- \rightarrow BiO(OH)\downarrow$$

If the insoluble substance is freshly precipitated by mixing hot, dilute solutions, there is only slight sedimentation on standing. This characteristic of magmas is sometimes enhanced by passing the product through a colloid mill.

For the most part, magmas are intended for internal use, although Bentonite Magma is used primarily as a suspending agent for insoluble substances either for local application or for internal use. All magmas require a label directing that they be shaken well before use. Freezing must be avoided.

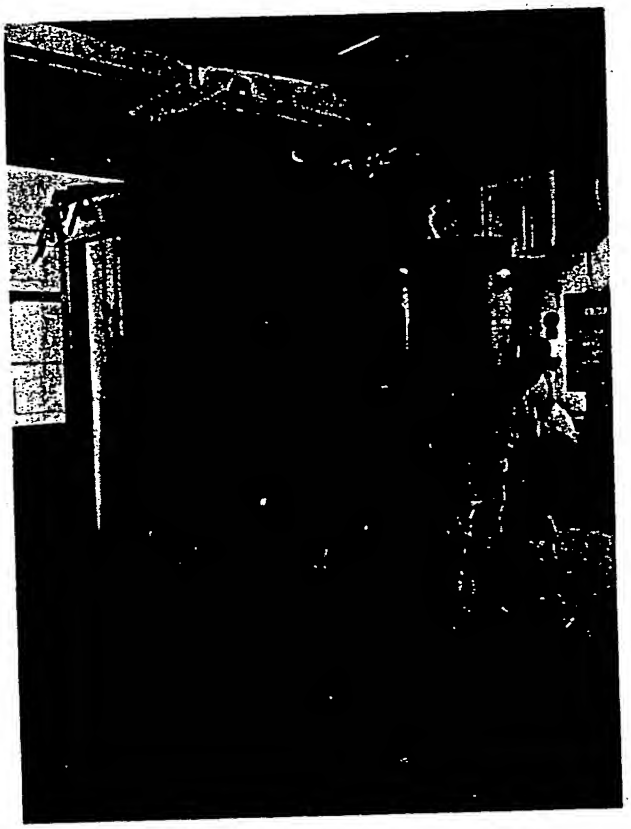


Fig. 83-9. This 5000-liter stainless steel tank is used in the final stages of production of an antacid suspension. The suspension is made to volume with filtered water, mixed, and pumped directly to an automatic bottle filler situated on a lower floor (courtesy, SK&F).

Gels

Pharmaceutical terminology is, at best, confusing and no two authors will classify Gels, Jellies, Magmas, Milks, and Mixtures in the same way. The NF described Gels as a special class of pharmaceutical preparations but considered Jellies under the same heading. The latter preparations usually contain water-soluble active ingredients and are, therefore, considered in another part of this chapter. The USP definition for Gels is given below.

Gels are semisolid systems of either suspensions made up of small inorganic particles or large organic molecules interpenetrated by a liquid. Where the gel mass consists of a network of small discrete particles, the gel is classified as a two-phase system (e.g., Aluminum Hydroxide Gel). In a two-phase system, if the particle size of the dispersed phase is relatively large, the gel mass is sometimes referred to as a magma (e.g. Bentonite Magma). Both gels and magmas may be thixotropic, forming semisolids on standing and becoming liquid on agitation. They should be shaken before use to ensure homogeneity and should be labeled to that effect.

Single-phase gels consist of organic macromolecules uniformly distributed throughout a liquid in such a manner that no apparent boundaries exist between the dispersed macromolecules and the liquid. Single-phase gels may be made from synthetic macromolecules (e.g., Carbomer) or from natural gums (e.g., Tragacanth). The latter preparations are also called mucilages. Although these gels are commonly aqueous, alcohol and oils may be used as the continuous phase. For example, mineral oil can be combined with a polyethylene resin to form an oleaginous ointment base.

The USP states that each 100 g of Aluminum Hydroxide Gel contains the equivalent of not less than 3.6 and not more than 4.4 g of aluminum oxide (Al_2O_3), in the form of aluminum hydroxide and hydrated oxide, and it may contain varying quantities of basic aluminum carbonate and bicarbonate. The gel itself is usually prepared by the interaction of a soluble aluminum salt, such as a chloride or sulfate, with ammonia solution, sodium carbonate or bicarbonate. The reactions which occur during the preparation are:

$$3CO_3^{=} + 3H_2O \rightarrow 3HCO_3^- + 3OH^-$$

$$[Al(H_2O)_6]^{+++} + 3OH^- \rightarrow [Al(H_2O)_3(OH)_3]\downarrow + 3H_2O$$

$$2HCO_3^- \rightarrow CO_3^{=} H_2O + CO_2\uparrow$$

The physical and chemical properties of the gel will be affected by the order of addition of reactants, pH of precipitation, temperature of precipitation, concentration of the reactants, the reactants used, and the conditions of aging of the precipitated gel.

Aluminum Hydroxide Gel is soluble in acidic (or very strongly basic) media. The mechanism in acidic media is:

$$\text{Aluminum Hydroxide Gel} + 3H_2O \rightarrow [Al(H_2O)_3(OH)_3]^\circ$$

$$[Al(H_2O)_3(OH)_3]^\circ + H_3O^+ \rightarrow [Al(H_2O)_4(OH)_2]^+ + H_2O$$

$$[Al(H_2O)_4(OH)_2]^+ + H_3O^+ \rightarrow [Al(H_2O)_5(OH)]^{++} + H_2O$$

$$[Al(H_2O)_5(OH)]^{++} + H_3O^+ \rightarrow [Al(H_2O)_6]^{+++} + H_2O$$

It is unlikely that the last reaction given proceeds to completion. Since the activity of the gel is controlled by its insolubility (solution will decrease with an increase in the pH of the gastric media), there is no acid rebound. Further, since a certain quantity of insoluble gel is always available, the neutralizing capability of the gel extends over a considerable period of time.

Aluminum hydroxide gels may also contain peppermint oil, glycerin, sorbitol, sucrose, saccharin, and various preservatives. Sorbitol improves the acid-consuming capacity, apparently by inhibiting a secondary polymerization that takes place on aging. Certain active ingredients are often added to the gel to enhance its use as an antacid preparation. One such formulation is:

Aluminum Hydroxide and Belladonna Mixture BPC

Belladonna Tincture	100 ml
Chloroform Spirit	50 ml
Aluminum Hydroxide Gel to	1000 ml

It should be noted, however, that the addition of other drugs (e.g., antibiotics) to the gel may result in a loss of the activity anticipated for that active ingredient.

Generally, if left undisturbed for some time, gels may become semisolid or gelatinous. With some gels, small amounts of water may separate on standing.

Lotions

Lotions are usually liquid suspensions or dispersions intended for external application to the body. They may be prepared by triturating the ingredients to a smooth paste and then cautiously adding the remaining liquid phase. High-speed mixers or homogenizers produce better dispersions and are, therefore, the tools of choice in the preparation of larger quantities of lotion. Calamine Lotion USP is the classical example of this type of preparation and consists of finely powdered, insoluble solids held in more or less permanent suspension by the presence of suspending agents and/or surface-active agents. Many investigators have studied Calamine Lotion and this had led to the publication of many formulations, each possessing certain advantages over the others but none satisfying the collective needs of all dermatologists. The formula for the official lotion is given on page 722.

Phenolated Calamine Lotion USP (page 722) contains 10 ml of liquefied phenol in sufficient calamine lotion to make the product measure 1000 ml. Formulations containing Avicel R (hydrated microcrystalline cellulose, *Am. Viscose*) and carboxymethylcellulose settle less than do the official preparations.

Mixtures

The official mixtures are aqueous liquid preparations which contain suspended, insoluble, solid substances and are intended for internal use. The insoluble substance does not make the mixture very viscous and the particles may be held in suspension by the use of suitable suspending or thickening agents. This class was originally introduced to secure uniformity in the formulas of certain well-known and largely used preparations. Frequently the term *mixture* is applied loosely to aqueous preparations of every description. The term *shake mixture* is often used for liquid preparations which contain insoluble ingredients and must, therefore, be shaken before use. The USP does not recognize the term. The term *suspension* is now used to describe a number of similar preparations. The BPC uses the term *mixtures* and includes suspensions in this category.

The pectin and the tragacanth in Kaolin Mixture with Pectin (page 753) act as suspending agents. An alternate formula, based on Veegum (*Vanderbilt*) and sodium carboxymethylcellulose, has been proposed.[18]

Kaolin Mixture with Pectin

Veegum	0.88 g
Sodium Carboxymethylcellulose	0.22 g
Purified Water	79.12 g
Kaolin	17.50 g
Pectin	0.44 g
Saccharin	0.09 g
Glycerin	1.75 g

Add the Veegum and the sodium carboxymethylcellulose to the water with continuous stirring. Add, with mixing, the kaolin. Mix the pectin, the saccharin, and the glycerin and add to the suspension. A preservative and a flavoring agent may be added to the product.

Brown Mixture NF XII contains glycyrrhiza fluidextract, antimony potassium tartrate, paregoric, alcohol, glycerin, and water. A precipitate is formed when the major ingredients in the formula, glycyrrhiza fluidextract and paregoric, are combined.

The insoluble material in mixtures must be in a very finely divided state and it must be uniformly distributed throughout the preparation. This is accomplished by the use of colloid mills, special methods of precipitation, and suspending agents. There are three main reasons for having the insoluble substances in as fine a state of subdivision as possible.

1. The more nearly the colloidal state is approached by protectives, such as kaolin, magnesium trisilicate, and magnesium phosphate, the more active they become as adsorbents and protectives when in contact with inflamed surfaces.
2. Finely divided particles are suspended more readily and settle out much more slowly than large particles, thus enabling the patient to obtain uniform doses of suspended substances. Homogeneous mixtures are especially desirable when administering medication to form an evenly distributed, protective coating on the gastrointestinal tract.
3. The palatability of many preparations is enhanced by the use of colloidal suspending agents.

Mixtures containing suspended material should have a "Shake Well" label affixed to the container in which they are dispensed.

Mixtures, including suspensions, are subject to contamination by microorganisms that remain viable and are a potential health hazard during the period of use of the products. Survival times of organisms depend on the preservative used in the formulation. A kaolin pediatric mixture that contains benzoic acid kills organisms rapidly, whereas organisms survived for more than a week in a magnesium trisilicate mixture that contained no more than a trace of peppermint oil.[19]

Official Suspensions

The USP places particular emphasis on the term suspension by providing specific definitions for a variety of oral, parenteral, and ophthalmic preparations formulated in such a way that an insoluble substance is suspended in a liquid at some stage of the manufacturing or dispensing process. The USP definition begins as follows:

> Suspensions are preparations of finely divided, undissolved drugs dispersed in liquid vehicles. Powders for suspension are preparations of finely powdered drugs intended for suspension in liquid vehicles. An example of the ready-to-use type is *Trisulfapyrimidines Oral Suspension*, in which the three sulfapyrimidines are already suspended in a liquid, flavored vehicle in a form suitable for oral administration. *Tetracycline for Oral Suspension* is finely divided tetracycline mixed with suspending and dispersing agents. It is intended to be constituted with the prescribed volume of purified water and mixed before it is dispensed by the pharmacist for oral administration to the patient.

Neither this definition nor the monographs give specific directions for the preparation of the suspension although pharmacopeias usually permit the addition of suitable flavoring agents, suspending agents, preservatives, and certified color additives. One procedure for the preparation of the commonly used *Trisulfapyrimidines Oral Suspension* is given below.

Trisulfapyrimidines Oral Suspension

Veegum	1.00 g
Syrup USP	90.60 g
Sodium Citrate	0.78 g
Sulfadiazine	2.54 g
Sulfamerazine	2.54 g
Sulfamethazine	2.54 g

Add the Veegum, slowly and with continuous stirring, to the syrup. Incorporate the sodium citrate into the Veegum-syrup mixture. Premix the sulfa drugs and add to the syrup. Stir and homogenize. Add sufficient 5% citric acid to adjust the pH of the product to 5.6. A preservative and a flavoring agent may be added to the product.

Methods of preparation for those formulations which contain several active ingredients and are produced in large quantities tend to be more complex than that given above.

Many formulations for suspensions are given in the BPC under the heading of *mixtures*. A properly prepared suspension has a number of desirable properties: (a) the suspended material should not settle rapidly; (b) particles that do settle should not form a hard cake and should easily be uniformly resuspended on shaking; (c) the suspension should pour freely from the container. Insoluble powders that do not disperse evenly throughout the suspending medium, when shaken, should be finely powdered and levigated with a small amount of an agent such as glycerin or alcohol or a portion of the dispersion of the suspending agent. The other ingredients are incorporated and the remainder of the dispersion of the suspending agent is gradually incorporated by trituration to produce the appropriate volume.

Suspensions intended for parenteral or ophthalmic use are also described in the USP. For a discussion of these suspensions, reference should be made to Chapters 84 and 86.

Extraction

Extraction, as the term is used pharmaceutically, involves the separation of medicinally active portions of plant or animal tissues from the inactive or inert components by use of selective solvents in standard extraction procedures. The products so obtained from plants are relatively impure liquids, semisolids, or powders, intended only for oral or external use; they include classes of preparations known as decoctions, infusions, fluidextracts, tinctures, pilular (semisolid) extracts and powdered extracts. Such preparations have been popularly called galenicals, after Galen, the 2nd century Greek physician. For additional information concerning extraction and extractives, which are briefly discussed in the following, see RPS 15, Chapter 86.

In this discussion we are concerned primarily with basic extraction procedures for crude drugs to obtain the therapeutically desirable portion and eliminate the inert material by treatment with a selective solvent, known as the menstruum. Extraction differs from solution in that the presence of insoluble matter is implied in the former process. The principal methods of extraction are: (1) maceration, (2) percolation, (3) digestion, (4) infusion, and (5) decoction.

The processes of particular importance, insofar as official compendia are concerned, are those of maceration and percolation; most pharmacopeias refer to such processes for extraction of active principles from crude drugs.

Maceration—In this process the solid ingredients are placed in a stoppered container with the whole of the solvent and allowed to stand for a period of at least three days (until soluble matter is dissolved), with frequent agitation. The mixture is then strained, the marc (the damp solid material) pressed, and the combined liquids are clarified by filtration or by decantation after standing.

Percolation—This is the procedure most frequently used to extract the active ingredients in the preparation of tinctures and fluidextracts. Certain procedural details have been provided in US official compendia, which should be consulted for such information. In the BPC general procedure a percolator (a narrow cone-shaped vessel open at both ends) is used. The solid ingredient(s) are moistened with an appropriate amount of specified menstruum and allowed to stand for approximately four hours in a well-closed container, after which the drug mass is packed into the percolator. Sufficient menstruum is added to saturate the mass and the top of the percolator is closed. When the liquid is about to drip from the neck (bottom) of the percolator, the outlet is closed. Additional menstruum is added to give a shallow layer above the mass and the mixture is allowed to macerate in the closed percolator for 24 hours. The outlet of the percolator is then opened and the liquid contained therein is allowed to drip slowly, additional menstruum being added as required, until the percolate measures about three-quarters of the required volume of the finished product. The marc is pressed and the expressed liquid is added to the percolate. Sufficient menstruum is added to produce the required volume, and the mixed liquid is clarified by filtration or by allowing it to stand and then decanting.

For a detailed discussion of various aspects of percolation see RPS 15, Chapter 86.

Digestion—This is a form of maceration in which *gentle heat* is used during the process of extraction. It is used when moderately elevated temperature is not objectionable and the solvent efficiency of the menstruum is increased thereby.

Infusion—An infusion is a dilute solution of the readily soluble constituents of crude drugs. Fresh infusions are prepared by macerating the drugs for a short period of time with either cold or boiling water. US official compendia have not included infusions for some time. An example is Concentrated Compound Gentian Infusion BP 1973.

Decoction—This once-popular process extracts water-soluble and heat-stable constituents from crude drugs by boiling in water for 15 minutes, cooling, straining, and passing sufficient cold water through the drug to produce the required volume.

Extractives

After a solution of the active constituents of a crude drug is obtained by maceration or percolation, it may be ready for use as a medicinal agent, as with certain tinctures or fluidextracts, or it may be further processed to produce a solid or semisolid extract. Information concerning these three classes of extractive preparations follows.*

Tinctures—Tinctures are defined in the USP as being alcoholic or hydroalcoholic solutions prepared from vegetable materials or from chemical substances, an example of the latter being Iodine Tincture. Traditionally, tinctures of potent vegetable drugs essentially represent the activity of 10 g of the drug in each 100 ml of tincture, the potency being adjusted following assay. Most other tinctures of vegetable drugs represent the extractive from 20 g of the drug in 100 ml of tincture.

The US official compendia have described two general processes for preparing tinctures, one by percolation designated as Process P, and the other by maceration designated as Process M. These utilize the methods described above, on this page. Process P includes a modification so that tinctures that require assay for adjustment to specified potency may be thus tested before dilution to final volume. A tincture prepared by Process P as modified for assayed tinctures is Belladonna Tincture. Examples of tinctures prepared by Process M are Compound Benzoin Tincture and Sweet Orange Peel Tincture (the latter contains the extractive from 50 g of sweet orange peel in 100 ml of tincture).

Fluidextracts—The USP defines fluidextracts as being liquid preparations of vegetable drugs, containing alcohol as a solvent or as a preservative, or both, so made that each ml contains the therapeutic constituents of 1 g of the standard drug that it represents. While the USP states that pharmacopeial fluidextracts are made by percolation, the official compendia have long described general procedures for three percolation methods used in making fluidextracts. Process A is a percolation method that can be modified for fluidextracts that must be assayed. Process E is an alternative for Process A in which percolation is conducted on a column of drug much greater in length than in diameter. Process D is used for preparing fluidextracts with boiling water as the menstruum, alcohol being added as a preservative to the concentrated percolate; this is the procedure used for preparing Cascara Sagrada Fluidextract.

The BP and BPC use the designation *Liquid Extracts* for the category of fluidextracts.

Extracts—Extracts are defined by USP as concentrated preparations of vegetable or animal drugs obtained by removal of the active constituents of the respective drugs with suitable

* For a discussion of *resins* and *oleoresins* obtained by solvent extraction of plant exudates see Chapter 25, under *Plant Exudates*.

menstrua, evaporation of all or nearly all of the solvent, and adjustment of the residual masses or powders to the prescribed standards.

Three forms of extracts are recognized: semiliquids or liquids of syrupy consistency; plastic masses, known as *pilular* or *solid extracts*; and dry powders, known as *powdered extracts*. Extracts, as concentrated forms of the drugs from which they are prepared, are used in a variety of solid or semisolid dosage forms. The USP states that pilular extracts and powdered extracts of any one drug are interchangeable medicinally, but each has its own pharmaceutical advantages. Pilular extracts, so-called because they are of a consistency that they could be used in pill masses and made into pills, are especially suited for use in ointments and suppositories; powdered extracts are better suited for incorporation into a powdered formulation, as in capsules, powders, or tablets. Semiliquid extracts or extracts of a syrupy consistency may be used in the manufacture of some pharmaceutical preparations.

Most extracts are prepared by extracting the drug by percolation. The percolate is concentrated, generally by distillation under reduced pressure; use of heat is avoided where possible because of potential injurious effect on active constituents. Powdered extracts that are made from drugs that contain inactive oily or fatty matter may have to be defatted or prepared from defatted drug. For diluents that may be used to adjust an extract to prescribed standards, see the USP.

Pure Glycyrrhiza Extract USP is an example of a pilular extract; Belladonna Extract USP and Hyoscyamus Extract BPC are examples of powdered extracts (the former is prepared also as a pilular extract and the latter as a liquid extract).

References

1. Ostendorf JP. *J Soc Cosmet Chem 16:* 203, 1965.
2. Bruch CW. *Drug Cosmetic Ind 111*(4): 51, 1972.
3. Hickman K, *et al. Science 180:* 15, 1973.
4. Taylor SL, *et al. Appl Microbiol 20*(5): 720, 1970.
5. Meer T: *Flavoring Pharmaceutical Preparations* (SK&F Selected Pharm Res Refs No. 4) SK&F, Philadelphia, Feb. 11, 1957.
6. Boehm EE, Maddox DN. *Manuf Chem Aerosol News 43:* Aug. 21, 1972.
7. Hutchins HH, Singiser RE. *J Am Pharm Assoc Pract Pharm Ed 16:* 226, 1955.
8. Sumner ED. *J Am Pharm Assoc NS8:* 250, 1968.
9. Fraser JG. *J Laryngol 84:* 1055, 1970.
10. Ecker V, Fisher E. *Harokeach Haivri 13:* 350, 1969, through *Inter Pharm Abstr 7:* 4241, 1970.
11. Griffin WC, *et al. Drug Cosmetic Ind 102:* 41, 1967.
12. Becher P. *Emulsions: Theory and Practice,* Reinhold, New York, 267, 1965.
13. Peck GE, *et al. J Am Pharm Assoc Sci Ed 49:* 75, 1960.
14. Clayton W: *The Theory of Emulsions and Their Technical Treatment,* 3rd ed., Blakiston, Philadelphia, 294, 1935.
15. Chong CW. *J Soc Cosmet Chem 14:* 123, 1963.
16. Coffman HL, Huyck CL. *Am J Hosp Pharm 20:* 132, 1963.
17. Harb NA. *Cosmet Perfum 89:* 67, April 1974 through *Inter Pharm Abstr 11:* 3304, 1974.
18. Kalish J. *Drug Cosmet Ind 94:* 279, 1964.
19. Westwood N. *Pharm J 208:* 153, 1972.

Chapter 84

Parenteral Preparations

history
administration
components
production
quality control
packaging
labeling

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The term parenteral (Gk, *para enteron* = beside the intestine) refers to the route of administration of drugs by injection under or through one or more layers of skin or mucous membrane. Since this route circumvents the highly efficient protective barriers of the human body, the skin and mucous membranes, exceptional purity of the dosage form must be achieved. The processes utilized in preparing the dosage form must embody good manufacturing practices that will produce and maintain the required quality of the product. New developments in process technology and quality control should be adopted as soon as their value and reliability have been established as a means for further improving the quality of the product.

History[1]

One of the most significant events in the beginnings of parenteral therapy was the first recorded injection of drugs into the veins of living animals, in about the year 1657, by the architect Sir Christopher Wren. From such a very crude beginning, the technique for intravenous injection and knowledge of the implications thereof developed slowly during the next century and a half. During the first half of the 19th century, the subcutaneous route of administration was being developed. In 1855 Dr. Alexander Wood of Edinburgh described what was probably the first subcutaneous injection of drugs for therapeutic purposes using a true hypodermic syringe.

The latter half of the 19th century brought increasing concern for safety in the administration of parenteral solutions, largely because of the work of Robert Koch and Louis Pasteur. While Charles Chamberland was developing both hot-air and steam sterilization techniques and the first bacteria-retaining filter (made of unglazed porcelain), H. Nordtmeyer was developing a filter made of kieselguhr (the Berkefeld filter), and Stanislaus Limousin was developing a suitable container, the all-glass ampul. Shortly after the beginning of the 20th century, attention focused on the disturbing chills and fever which often followed the intravenous injection of drugs. In the middle 1920s Dr. Florence Seibert provided proof that this reaction was caused by potent products of microbial growth, pyrogens, which could be eliminated from water by distillation and from glassware by heating at elevated temperatures. These developments were prominent among those that provided the foundation for increasing use of parenteral routes for the administration of drugs.

Administration

Injections may be classified in five general categories: (1) solutions ready for injection, (2) dry, soluble products ready to be combined with a solvent just prior to use, (3) suspensions ready for injection, (4) dry, insoluble products ready to be combined with a vehicle just prior to use, and (5) emulsions. These injections may be administered by such routes as intravenous, subcutaneous, intradermal, intramuscular, intraspinal, intracisternal, and intrathecal. The nature of the product will determine the particular route of administration that may be employed. Conversely, the desired route of administration will place requirements on the formulation. For example, suspensions would not be administered directly into the blood stream because of the danger of insoluble particles blocking capillaries. Solutions to be administered subcutaneously would require strict attention to tonicity adjustment, otherwise irritation of the plentiful supply of nerve endings in this anatomical area would give rise to pronounced pain. Injections intended for intraocular, intraspinal, intracisternal, and intrathecal administration require the highest purity standards because of the sensitivity of nerve tissue to irritant and toxic substances.

When compared with other dosage forms, injections possess select advantages. If immediate physiological action is needed from a drug, it usually can be provided by intravenous injection of an aqueous solution. Modification of the formulation or another route of injection can be used to slow the onset and prolong the action of the drug. The therapeutic response of a drug is more readily controlled by parenteral administration since the irregularities of intestinal absorption are circumvented. Also, since the drug normally is administered by a professionally trained person, it may be confidently expected that the dose was actually and accurately administered. Drugs can be administered parenterally when they cannot be given orally because of the unconscious or uncooperative state of the patient, or because of inactivation or lack of absorption in the intestinal tract. Among the disadvantages of this dosage form are the requirement of asepsis at administration, the risk of tissue toxicity from local irritation, the real or psychological pain factor, and the difficulty in correcting an error, should one be made. In the latter situation, unless a direct pharmacological antagonist is immediately available, correction of an error may be impossible. One other disadvantage is that daily or frequent administration poses difficulties, either for the patient to visit a professionally trained person or to learn to inject oneself.

Parenteral Combinations

Since there is a degree of discomfort for the patient with each injection, a physician will frequently seek to reduce this discomfort by combining more than one drug in one injection. This is most commonly encountered when therapeutic agents are added to large-volume solutions of electrolytes or nutrients, commonly called "IV additives," during intravenous administration. Since these preparations would be aqueous solutions, there is a high potential for chemical and physical interactions to occur. The pharmacist is the professional best qualified to cope with these incompatibilities. However, in the past, these have been handled largely at the patient's

bedside by the nurse and physician. Only recently has it been recognized that this professional area is the proper function of a pharmacist and has been so stated by the Joint Commission on Accreditation of Hospitals.[2]

As pharmacists have assumed increasing responsibility in this area, awareness has gradually developed of the widespread occurrence of visible, as well as invisible, physical, chemical, and therapeutic incompatibilities when certain drugs are combined or added to intravenous fluids.

Development of a precipitate or a color change when preparations are combined is an immediate warning that an alteration has occurred. Such a combination should not be administered to the patient because the solid particles may occlude the blood vessels, the therapeutic agent may not be available for absorption, or the drug may have been degraded into toxic substances. Moreover, in other instances changes not visually apparent may have occurred which could be equally or more dangerous to the welfare of the patient.

The almost innumerable potential combinations present a complex situation even for the pharmacist. In an attempt to organize the information available and to aid the pharmacist in making rapid decisions concerning potential problems, a number of charts have been compiled based on the visible changes that may be observed when two or more preparations are combined. The value of such charts is limited by such factors as frequent changes in commercial products, variations in order of mixing or the proportions in the mixture, differences in concentration of each ingredient, or variations in the period of time that the combination is held before use.

As studies have been undertaken and more information has been gained, it has been shown that knowledge of variable factors such as pH and the ionic character of the active constituents aids substantially in understanding and predicting potential incompatibilities. Kinetic studies of reaction rates may be utilized to describe or predict the extent of degradation. Ultimately, a thorough study should be undertaken of each therapeutic agent in combination with other drugs and intravenous fluids, not only of generic but of commercial preparations, from the physical, chemical, and therapeutic aspects. Such studies are being undertaken and some have been reported.

Ideally, no parenteral combination should be administered unless it has been thoroughly studied to determine the effect of the combination on the therapeutic value and the safety of each such combination. However, such an ideal situation does not and may never exist. Therefore, it is the responsibility of the pharmacist to be as familiar as possible with the physical, chemical, and therapeutic aspects of parenteral combinations and to exercise the best possible judgment as to whether or not the specific combination extemporaneously prescribed is suitable for use in a patient. A service to pharmacists has been provided through reviews of this subject area.[3]

General Requirements

An inherent requirement for parenteral preparations is that they be of the very best quality and provide the maximum safety for the patient. Therefore, the pharmacist, being responsible for their preparation, must utilize skills and resourcefulness at the highest level of efficiency to achieve this end. Among the areas requiring dedicated attention are the following:

1. Possession and application of high moral and professional ethics. Even the thought of using inferior techniques or ingredients in a manufacturing process must not be countenanced by the pharmacist. The proper attitude of the person responsible for the preparation of the product is its most vital ingredient.
2. The pharmaceutical training received must be utilized to the fullest measure. The challenges to this knowledge bank will be many and varied.
3. Specialized techniques will be required for the manufacture of sterile preparations, employing them with alertness and sound judgment. These techniques must be subjected to continuous critical review for faults, omissions, and improvements.
4. Ingredients of the highest quality obtainable must be utilized. At times ingredients may require special purification beyond that of the commercial supply. This will normally require that cost factors be given second place in importance.
5. The stability and effectiveness of the product must be established with substantiating data, either from original or published sources. This must take into account process variations and differences in ingredient specifications from plant to plant.
6. A well-defined and controlled program must be established to assure the quality of the product and the repetition of valid production procedures. This involves evaluation of all ingredients, vigilant controls of all steps in the production procedures, and careful evaluation of the finished product.

Injections or other sterile products are rarely prepared in the community pharmacy because of the lack of adequate facilities necessary to prepare a reliable and safe product.

In some hospital pharmacies injections or irrigating fluids are manufactured, but in an increasing number aseptic processing is utilized primarily in the addition of various drugs to intravenous solutions for the individual patient. The vast majority of injectable products used clinically are prepared by the pharmaceutical industry.

General Process

The preparation of a parenteral product may be considered to encompass four general areas as follows: (1) procurement and selection of the components, (2) production facilities and procedures, (3) control of quality, and (4) packaging and labeling. The components of the product to be procured include vehicles, solutes, containers, and closures. The steps constituting production include the maintenance of facilities and equipment, preparing and controlling the environment, cleaning the containers and equipment, preparing the product, filtering the solution, filling containers with the product, sealing the containers, and sterilizing the product. Control of quality includes the evaluation of the components, validation of equipment and processes, determination that the production has been executed within prescribed requirements, and performance of necessary evaluative tests on the finished product. The final area of packaging and labeling includes all steps necessary to identify the finished product and enclose it in such manner that it is safely and properly prepared for sale and delivery to the user. In the following sections, these four areas and appropriate subtopics will be discussed in detail.

Components and Containers

Establishing specifications to insure the quality of each of the components of an injection is of vital importance. These specifications will be coordinated with the requirements of the specific formulation and will not necessarily be identical for a particular component if used in several different formulations.

The most stringent requirements normally will be encountered with aqueous solutions, particularly if the product is to be sterilized at an elevated temperature where reaction rates will be greatly accelerated. Modification of aqueous vehicles to include a glycol, or replacement with a nonaqueous vehicle, will usually reduce reaction rates. Dry preparations pose relatively few reaction problems but may require definitive physical specifications for ingredients that must have certain solution or dispersion characteristics when a vehicle is added.

Containers and closures are herein considered components of the product because they are in prolonged, intimate contact with the product and may release substances or remove ingredients from the product. While not usually considered a part of a container, administration devices are a part of a container system and their effect upon the product must be assessed even though the contact period is usually brief.

Vehicles

Since most liquid injections are quite dilute, the component present in the highest proportion is the vehicle. A vehicle normally has no therapeutic activity and is nontoxic. However, it is of great importance in the formulation since it presents to body tissues the form of the active constituent for absorption. Absorption normally occurs most rapidly and completely when a drug is presented as an aqueous solution. Modification of the vehicle with water-miscible liquids or substitution with water-immiscible liquids normally decreases the rate of absorption. Absorption from a suspension may be affected by such factors as the viscosity of the vehicle, its capacity for wetting the solid particles, the solubility equilibrium produced by the vehicle, and the distribution coefficient between the vehicle and aqueous body systems.

The vehicle of greatest importance for parenteral products is water. Water of suitable quality for parenteral administration must be prepared either by distillation or by reverse osmosis. Only by these means is it possible to separate adequately various liquid, gas and solid contaminating substances from water.

Preparation of Water

In general, a conventional still consists of a boiler (evaporator) containing raw water (distilland), a source of heat to vaporize the water in the evaporator, a headspace above the level of distilland with condensing surfaces for refluxing the vapor and thereby returning nonvolatile impurities to the distilland, a means for eliminating volatile impurities before the hot water vapor is condensed, and a condenser for removing the heat of vaporization, thereby converting the water vapor to a liquid distillate.

It should be apparent that the specific construction features of a still and the process specifications will markedly affect the quality of distillate obtained from a still. Those required for producing high-purity water, such as Water for Injection USP, must be considerably more stringent than those required for Purified Water USP. Among the factors that must be considered are:

1. The quality of the raw water will affect the quality of the distillate. It may be necessary that the raw water be first deionized, treated by reverse osmosis or even distilled to obtain a final distillate of adequate quality.
2. The size of the evaporator will affect the efficiency. The evaporator should be large enough to provide a low vapor velocity, thus reducing entrainment of distilland either as a film on vapor bubbles or as separate droplets.
3. The baffles (condensing surfaces) determine the effectiveness of refluxing. They should be designed to efficiently remove entrainment at optimal vapor velocity, collecting and returning the heavier droplets contaminated with distilland.
4. Redissolving of volatile impurities in the distillate reduces purity. Therefore, volatile impurities should be separated efficiently from the hot water vapor and eliminated by aspirating to the drain or venting to the atmosphere.
5. Contamination of the vapor and distillate from the metal parts of the still can occur. Present standards for high-purity stills are that all parts contacted by the vapor or distillate should be constructed of metal coated with pure tin, of 304 or 316 stainless steel, or of chemically resistant glass.

Design features of a still also influence its efficiency of operation, relative freedom from maintenance problems, or the extent of automatic operation. Stills may be constructed of varying size, rated according to the volume of distillate that

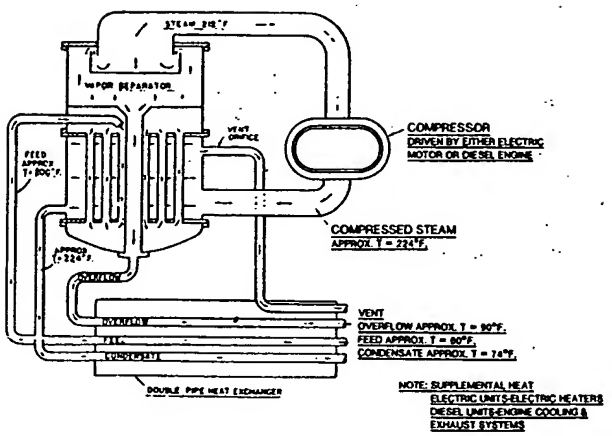

Fig. 84-1. Vapor compression still.

can be produced per hour of operation under optimum conditions. Only stills designed to produce high-purity water may be considered for use in the production of Water for Injection USP.

Conventional commercial stills designed for the production of high-purity water are available from several suppliers.*

Compression Distillation—The vapor compression still, primarily designed for the production of large volumes of high purity distillate with low consumption of energy and water, is illustrated diagrammatically in Fig. 84-1. To start, the feed water is heated in the evaporator to boiling. The vapor produced in the tubes is separated from entrained distilland in the separator and conveyed to a compressor which compresses the vapor and raises its temperature to approximately 224°F. It then flows to the steam chest where it condenses on the outer surfaces of the tubes containing distilland; thereby the vapor is condensed and drawn off as distillate while giving up its heat to bring the distilland in the tubes to the boiling point.

Vapor compression stills are available in capacities from 50 to 2800 gal/hour (*Aqua-Chem, Barnstead, Meco*). In addition to their use by the pharmaceutical industry, they are utilized extensively by military and governmental installations for the production of potable water from sea and brackish well water.

Reverse Osmosis—Reverse osmosis has recently been added by the USP as a method suitable for preparation of Water for Injection. As the name suggests, the natural process of selective permeation of molecules through a semipermeable membrane separating two aqueous solutions of different concentrations is reversed. Pressure, usually between 200 and 400 psig, is applied to overcome osmotic pressure and force pure water to permeate through the membrane. Membranes, usually composed of cellulose esters or polyamides, are selected to provide an efficient rejection of contaminant molecules in raw water. The molecules most difficult to remove are small inorganic molecules such as sodium chloride. Passage through two membranes in series is sometimes utilized to increase the efficiency of removal of these small molecules and to decrease the risk of structural failure of a membrane to remove other contaminants, such as bacteria and pyrogens (for additional information concerning reverse osmosis see under this title in Chapter 77, and Fig. 77-21, in that chapter; also the discussion under *Water* in Chapter 83).

Currently, extensive validation is being undertaken to determine whether, in fact, this method is capable of consistently producing high-purity water of a quality equal or superior to that producible by distillation.

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* *Am. Sterilizer, Barnstead, Consolidated, Corning, Finn-Aqua.*

Water for Injection USP

This is a high-purity water intended to be used as a vehicle for injectable preparations. Sterile Water for Injection USP is described in a separate monograph and differs in that it is intended as a packaged and sterilized product.

Storage—Water for Injection should be used immediately. This is usually not possible since the quantity required in production of a product must be accumulated over a period of time. When storage of water is necessary, the conditions for storage and subsequent delivery to the point of use must meet strict standards. Otherwise, recontamination may occur. To prevent such recontamination, Water for Injection should be collected in a scrupulously clean, closed system; in its simplest form, the outlet from the condenser should be connected directly to a closed storage tank. Such a system is shown in Fig. 84-2. To allow for changes in pressure during filling and emptying of the tank, an air vent should be provided through a filter so constructed that microorganisms and chemical vapors will be prevented from entering the tank. The material of construction for the tank and connecting lines should be of chemically resistant glass, of metal parts with a heavy internal coating of pure tin, or of 304 or 316 stainless steel.

Although water vapor should be sterile when condensed, contamination of distillate can occur even with a closed collection system. Therefore, if storage is to be at room temperature, it should not exceed 24 hours. For longer periods, the water must be kept under conditions that will prevent growth of microorganisms and ingress of other contaminants.

If small quantities of Water for Injection are to be collected and stored, clean, sterile bottles made of chemically resistant glass may be used. After filling, the bottles are sealed, sterilized by autoclaving and kept until needed. Intermediate quantities may be collected in closed tanks. In some instances storage is at room temperature with microbial growth controlled by use of an immersion ultraviolet lamp, as shown in Fig. 84-2. Most frequently, however, the water is held at an elevated temperature of about 80°C by means of steam-jacketed tanks, a temperature too high for microbial growth to occur. Where large quantities of water are needed in multiple locations in the plant, for example, in the production of large-volume parenterals, very sophisticated storage and distribution systems have been developed. Such systems encompass large jacketed stainless steel storage tanks, welded and insulated stainless steel pipes to circulate the water to remote points of use, piping systems designed with a continuous loop back to the tank with no "dead legs," stainless steel circulating pumps, and controls to be assured that the temperature of all water in the system remains within established limits.

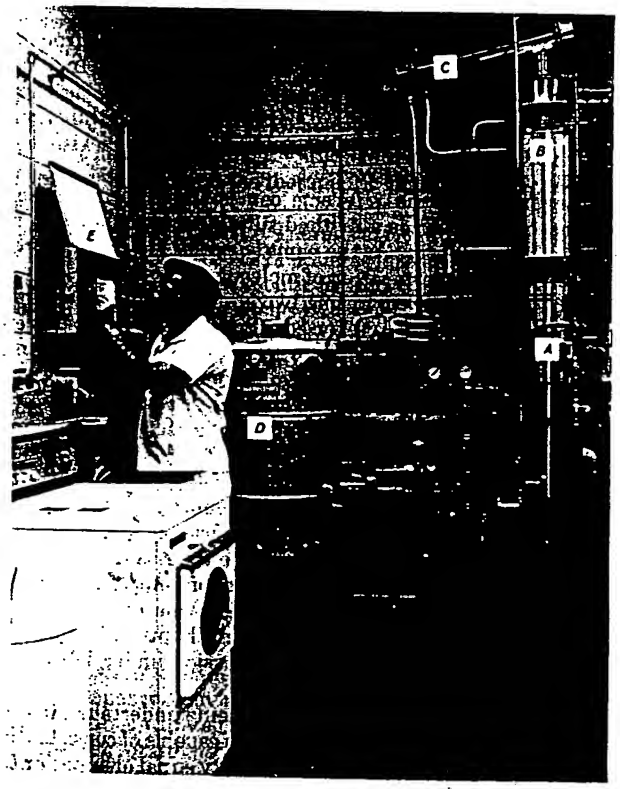

Fig. 84-2. High-purity still and sealed-water storage system. *A:* Evaporator; *B:* high-purity baffle unit; *C:* condenser; *D:* storage tank with ultraviolet lamp; *E:* control panel (courtesy, Ciba-Geigy).

When the water cannot be used at 80°C, heat exchangers must be installed to reduce the temperature at the point of use. Bacterial retentive filters should not be installed in such systems because of the risk of bacterial build-up on the filters and the consequential release of pyrogenic substances.

Purity—The USP monographs provide standards of purity for Water for Injection and for Sterile Water for Injection. A few of these standards require comment.

Sterile Water for Injection must meet the requirements of the USP Sterility Test, but Water for Injection need not since it is to be used in a product which will be sterilized. Both must meet the requirements of the USP Pyrogen Test (page 530).

The limits for total solids varies in the two monographs. The larger the surface area of the glass container per unit volume of water, the greater the amount of glass constituents that may be leached into the water, particularly during the elevated temperature of steam sterilization.

The Water for Injection monograph stipulates a maximum of 10 ppm of total solids. This is generally considered to be much too high to assure a quality of water that would permit stable formulation of many drugs. A relatively few metallic ions present can often render a formulation unstable. Therefore, it is common practice to set a limit of 0.1 ppm or less of ionic contaminants expressed as sodium chloride.

Ionic contaminant level is not the same as total solids, the former being a measurement of only the ionic content, while the latter is a measurement of undissociated constituents as well. The ionic content of water can be measured very easily by means of a conductivity meter, and is frequently used as an indication of the purity. The results are expressed in one of three terms; namely, as sodium chloride ions, as resistance in ohms or megohms, or as conductance in micromhos. Ohms and mhos have a reciprocal relationship to each other, but they are related to ppm sodium chloride by an experimentally determined curve. To give one point of comparison, 0.1 ppm sodium chloride is equal to approximately 1.01 megohms and 0.99 micromhos. It should be mentioned that conductivity measurements give no direct indication of pyrogen content of water since pyrogens are undissociated organic compounds.

Water for Injection may not contain an added substance. Sterile Water for Injection may contain a bacteriostatic agent when in containers of 30-ml capacity or smaller. This restriction is designed to prevent the administration of a large quantity of a bacteriostatic agent that probably would be toxic in the accumulated amount of a large volume of solution, even though the concentration was low.

Types of Vehicles

Aqueous Vehicles—Certain aqueous vehicles are recognized officially because of their valid use in parenteral formulations. Often they are used as isotonic vehicles to

a drug may be added at the time of administration. The additional osmotic effect of the drug may not be enough to produce any discomfort when administered. These vehicles include: Sodium Chloride Injection, Ringer's Injection, Dextrose Injection, Dextrose and Sodium Chloride Injection, and Lactated Ringer's Injection.

Water-Miscible Vehicles—A number of solvents that are miscible with water have been used as a portion of the vehicle in the formulation of parenterals. These solvents are used primarily to effect solubility of certain drugs and to reduce hydrolysis. The most important solvents in this group are ethyl alcohol, polyethylene glycol of the liquid series, and propylene glycol. Ethyl alcohol is used particularly in the preparation of solutions of cardiac glycosides and the glycols in solutions of barbiturates, certain alkaloids, and certain antibiotics. Such preparations are usually given intramuscularly.

These solvents, as well as nonaqueous vehicles, have been reviewed by Spiegel and Noseworthy.[4]

Nonaqueous Vehicles—The most important group of nonaqueous vehicles are the fixed oils. The USP provides specifications for such vehicles. A few of these requirements need to be discussed. The fixed oils must be of vegetable origin in order that they may be metabolized, will be liquid at room temperature, and will not become rancid rapidly. The first specification eliminates oils of mineral origin and the latter two, those of animal origin. To be liquid at room temperature, a fixed oil must contain esters of unsaturated fatty acids. However, excessive unsaturation will produce tissue irritation. Therefore, the USP stipulates upper and lower limits to the iodine value for the oil. The development of rancidity must be prevented by the inclusion of antioxidants such as tocopherol, a natural constituent of many fixed oils. The USP also prescribes an upper limit for free fatty acids in order to minimize the degree of tissue irritation. Other specifications are included primarily to detect adulteration. The oils most commonly used are corn oil, cottonseed oil, peanut oil, and sesame oil. It should be noted that the official monographs for some of these oils provide for greater latitude than the specifications required for the use of the oil as a vehicle for a parenteral. Therefore, parenteral vehicle oils must be select oils or specially purified to meet the more stringent requirements. Fixed oils are used particularly as vehicles for certain hormone preparations. These and other nonaqueous vehicles, such as ethyl oleate, isopropyl myristate and benzyl benzoate, may be used provided they are safe in the volume administered and do not interfere with the therapeutic efficacy of the preparation or with its response to prescribed assays and tests. The label also must state the name of the vehicle so that the user may beware in case of known sensitivity or other reactions to it.

Solutes

The requirements for purity of the medicinal compound ed in an injection often make it necessary to undertake cial purification of the usual chemical grade available. In few instances, a special parenteral grade of a compound is ailable, for example, ascorbic acid freed from all traces of pper contamination. As a general rule, the best chemical ade obtainable should be used. It should be obvious that few ppm of ionic contaminants in Water for Injection may se stability problems, a similar level of contamination in solute itself may, likewise, cause stability problems. tallic catalysis of chemical reactions is one of the most portant problems.

Other factors to be considered with respect to the quality olutes include: the level of microbial and pyrogenic conination, solubility characteristics as determined by the chemical or physical form of the compound, and freedom from gross dirt.

Added Substances—The USP includes in this category all substances added to a preparation to improve or safeguard the quality of the product. An added substance may effect solubility, as does sodium benzoate in Caffeine and Sodium Benzoate Injection, or provide patient comfort, as do substances added to make a solution isotonic. They may enhance the chemical stability of a solution, as do antioxidants, inert gases, chelating agents, and buffers, or they may preserve a preparation against the growth of microorganisms. The term "preservative" is sometimes applied only to those substances which prevent the growth of microorganisms in a preparation. However, such limited use is inappropriate, being better used for all substances that act to retard or prevent the chemical, physical, or biological degradation of a preparation.

While added substances may prevent a certain reaction from taking place, they may induce others. Not only may visible incompatibilities occur, but hydrolysis, complexation, oxidation, and other invisible reactions may decompose or otherwise inactivate the therapeutic agent. Therefore, added substances must be selected with due consideration and investigation of the effect of the substance on the total formulation.

Antimicrobial Agents—The USP states that antimicrobial agents in bacteriostatic or fungistatic concentrations must be added to preparations contained in multiple-dose containers. They must be present in adequate concentration at the time of use to prevent the multiplication of microorganisms inadvertently introduced into the preparation while withdrawing a portion of the contents with a hypodermic needle and syringe. Among the compounds most frequently employed, with the concentration limit prescribed by the USP, are: phenylmercuric nitrate and thimerosal 0.01%, benzethonium chloride and benzalkonium chloride 0.01%, phenol or cresol 0.5%, and chlorobutanol 0.5%. The above limit is rarely used for phenylmercuric nitrate, being most frequently employed in a concentration of 0.002%. Methyl *p*-hydroxybenzoate 0.18% and propyl *p*-hydroxybenzoate 0.02% in combination, and benzyl alcohol 2% are also frequently used. In oleaginous preparations, no antibacterial agent commonly employed appears to be effective. However, it has been reported that hexylresorcinol 0.5% and phenylmercuric benzoate 0.1% are moderately bactericidal.

Antimicrobial agents must be studied with respect to compatibility with all other components of the formula. In addition, their activity must be evaluated in the total formula. It is not uncommon to find that a particular agent will be effective in one formulation but ineffective in another. This may be due to the effect of various components of the formula on the biological activity or availability of the compound; for example, the binding and inactivation of esters of *p*-hydroxybenzoic acid by macromolecules such as Polysorbate 80 or the reduction of phenylmercuric nitrate by sulfide residues in rubber closures. A physical reaction encountered is that bacteriostatic agents are sometimes removed from solution by rubber closures. These facts establish the principle that antimicrobial agents must be evaluated for their activity in the total formula to assure their activity when needed, normally at the time of use.

Buffers—Buffers are used primarily to stabilize a solution against the chemical degradation that would occur if the pH changed appreciably. Buffer systems employed should normally have as low a buffer capacity as feasible in order not to disturb significantly the body buffer systems when injected. In addition, the buffer range and the effect of the buffer on the activity of the product must be evaluated carefully. The acid salts most frequently employed as buffers are citrates, acetates, and phosphates.

Antioxidants—Antioxidants are frequently required to

preserve products because of the ease with which many drugs are oxidized. Sodium bisulfite 0.1% is most frequently used. The use of sulfites as antioxidants has been reviewed by Schroeter[5]. Acetone sodium bisulfite, sodium formaldehyde sulfoxylate, and thiourea are also sometimes used. The sodium salt of ethylenediaminetetraacetic acid has been found to enhance the activity of antioxidants in some cases, apparently by chelating metallic ions that would otherwise catalyze the oxidation reaction.

Pyrogens

Pyrogens may be anticipated contaminants in crude drugs, such as antibiotics produced by fermentation, or they may be present as unexpected and unwanted contaminants in a finished product as a result of inadvertent contamination during processing. In the former instance, they must be eliminated during the purification steps of the drug. In the latter instance, they can best be eliminated by preventing their introduction during the process. In general, the presence of pyrogens in a finished product is indicative of a product prepared under inadequately controlled conditions.

Pyrogens cause a febrile reaction in human beings. Other symptoms include chills, pains in back and legs, and malaise. While pyrogens are rarely fatal, they produce significant discomfort for the patient. On the other hand, pyrogens have been shown to induce a general nonspecific resistance to microorganisms and, on this basis, have been used therapeutically.

Pyrogens are products of the growth of microorganisms. The most potent pyrogenic substances are produced by gram-negative bacteria, but gram-positive bacteria and fungi also produce pyrogenic substances. The potency varies with the species producing it. Chemically, pyrogenic material has been shown to be lipid in nature, sometimes containing phosphorus, and is attached to a polysaccharide or a protein or both. When so complexed, it is a weak antigen. A temporary tolerance to pyrogens will develop in man and susceptible animals.

Pyrogens can be destroyed by heating at high temperatures. The recommended procedure for depyrogenation of glassware and equipment is heating at a temperature of 250°C for 45 min. It has been reported that 650°C for 1 min or 180°C for 4 hours likewise will destroy pyrogens. The usual autoclaving cycle will not do so. Heating with strong alkali or oxidizing solutions will destroy pyrogens. It has been claimed that thorough washing with detergent treatment will render glassware pyrogen-free if it has been protected during manufacture and storage from heavy pyrogenic contamination. Likewise, plastic containers and devices must be protected from pyrogenic contamination during manufacture and storage since known ways to destroy pyrogens will adversely affect the plastic. It has been reported that anion exchange resins will adsorb pyrogens from water and reverse osmosis will eliminate them. However, the most reliable method for the elimination of these substances from water is distillation. Pyrogenic substances are not volatile and thus will remain in the distilland.

A method that has been used for the removal of pyrogens from solutions is adsorption on adsorptive agents. However, since the adsorption phenomenon may also cause selective removal of chemical substances from the solution and the filtrate may be contaminated with the agent, this method has limited application. Other in-process methods for the destruction or elimination of pyrogens include selective extraction procedures and careful heating with dilute alkali, dilute acid, or mild oxidizing agents. In each instance, the method must be thoroughly studied to be sure it will not have an adverse effect on the constituents of the product.

Sources of Pyrogens—Pyrogens may enter a preparation by any means that will introduce living or dead microorganisms or the products of their growth. Perhaps the greatest potential source of such contamination is the water used in products. Although proper distillation will provide pyrogen-free water, storage conditions must be such that microorganisms are not introduced and subsequent growth is prevented.

Another potential source of contamination is equipment. Pyrogenic materials adhere strongly to glass and other surfaces. Reusing containers, as is sometimes practiced in hospitals, may be a significant source of pyrogenic contamination. Residues of solutions in used bottles often become bacterial cultures from septic patients or the environment. Such bottles will be heavily contaminated with pyrogens. Even washed bottles left wet and exposed to the atmosphere may contain sufficient nutrients for microorganisms to grow. Since drying does not destroy pyrogens, they may remain in equipment for long periods of time. Adequate washing accompanied by dry-heat depyrogenation will render contaminated equipment suitable for use.

The solute also may be a source of pyrogens. Solutes may be crystallized or precipitated from aqueous liquids containing pyrogenic contamination. In the process pyrogens may be trapped within the particle layers. In such cases the solute must be purified by recrystallization, precipitate washing, or other means to eliminate the pyrogens.

The manufacturing process also must be carried out with great care and as rapidly as possible to minimize the risk of microbial contamination. Preferably, no more product should be prepared than can be completely processed within one working day, including sterilization.

Containers

Containers are an integral part of the formulation of an injection and may be considered a component, for there is no container that is totally insoluble or does not in some way affect the liquid it contains, particularly if the liquid is aqueous. Therefore, the selection of a container for a particular injection must be based on a consideration of the composition of the container, as well as of the solution, and the treatment to which it will be subjected.

Plastic

Thermoplastic polymers are increasingly finding a role as packaging materials for sterile preparations such as large volume parenterals and ophthalmic solutions. For this to be acceptable, an understanding of the characteristics, potential problems, and advantages for use must be developed. One thorough review of these factors relative to pharmaceutics has been prepared by Autian.[6] He stated that three principal problem areas exist in utilization of these materials, namely (1) permeation of vapors and other molecules in either direction through the wall of the plastic container, (2) leaching of constituents from the plastic into the product, and (3) sorption (absorption and/or adsorption) of drug molecules ions on the plastic material. Permeation may be troublesome by permitting volatile constituents or selected drug molecules to migrate through the wall of the container to the outside and thereby be lost. The reverse of this also may occur by which oxygen or other gases may permeate to the inside of the container and cause oxidative degradation of susceptible constituents. Leaching may be a problem when certain constituents of the plastic material migrate into the product particularly aqueous preparations. This potential problem may be controlled by careful formulation of the polymer mixture with a minimum of additives. Sorption seems to be a limited problem in the packaging of parenterals and is most commonly in association with polyamides such as nylon.

In the use of plastic packaging materials, one of the principal advantages is that such materials are not breakable as is glass. In addition, there is a substantial reduction in weight. The flexibility of the low-density polyethylene polymer, for ophthalmic preparations, makes it possible to squeeze the side wall of the container and discharge one or more drops without introducing contamination into the remainder of the preparation. The flexible bags of polyvinyl chloride or select polyolefins, currently in use for large-volume intravenous fluids, have the added advantage that no air interchange is required; the flexible wall of the bag simply collapses as the solution flows out of the bag.

Most plastic materials have the disadvantage that they are not as clear as glass and, therefore, inspection of the contents is impeded. In addition, many of these materials will soften or melt under the conditions of thermal sterilization. However, careful selection of the plastic utilized and control of the autoclave cycle has made thermal sterilization of some products possible, large volume parenterals in particular. Ethylene oxide sterilization may be employed for the empty container with subsequent aseptic filling of the product. However, careful evaluation of the residues from ethylene oxide and their potential toxic effect must be undertaken.

Because of the relatively new use of plastic materials for packaging sterile preparations, considerable investigation is still required concerning potential interactions and other problems that may be encountered. For further details see Chapter 80.

Glass

Glass is employed as the container material of choice for most injections. It is composed principally of silicon dioxide with varying amounts of other oxides such as those of sodium, potassium, calcium, magnesium, aluminum, boron, and iron. The basic structural network of glass is formed by the silicon oxide tetrahedron.[7] Boric oxide will enter into this structure, but most of the other oxides do not. The latter are only loosely bound, are present in the network interstices, and are relatively free to migrate. These migratory oxides may be leached into a solution in contact with the glass, particularly during the increased reactivity of thermal sterilization. The oxides thus dissolved may hydrolyze to raise the pH of the solution, catalyze reactions, or enter into reactions. In a manner as yet uncertain, some glass compounds will be attacked by solutions and, in time, dislodge glass flakes into the solution. Disturbing reactions such as these can, however, be minimized by the proper selection of the glass composition.

Types—The USP has aided in this selection by providing a classification of glass; namely, Type I, a borosilicate glass; Type II, a soda-lime treated glass; Type III, a soda-lime glass; and NP, a soda-lime glass not suitable for containers for parenterals. Type I glass is composed principally of silicon dioxide and boric oxide, with low levels of the nonnetwork-forming oxides. It is a chemically resistant glass (low leachability) also having a low thermal coefficient of expansion. Type II and Type III glass compounds are composed of relatively high proportions of sodium oxide and calcium oxide. This makes the glass chemically less resistant. Both of these types melt at a lower temperature, are easier to mold into various shapes, and have a higher thermal coefficient of expansion than Type I. While there is no one standard formulation for glass among manufacturers of these USP type categories, Type II glass usually has a lower concentration of the migratory oxides than Type III. In addition, Type II glass has been treated under controlled temperature and humidity conditions with sulfur dioxide to dealkalize the internal surface of the container. While it remains intact, this surface will substantially increase the chemical resistance of the glass.

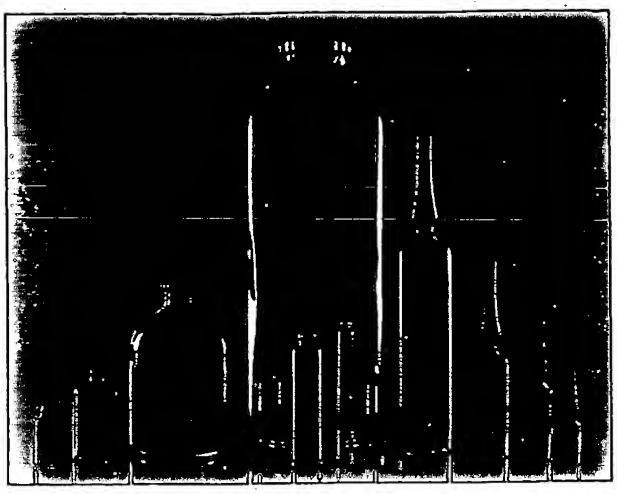

Fig. 84-3. Various types of ampuls and multiple-dose vials for parenterals (courtesy, Kimble).

However, repeated exposures to sterilization procedures and to alkaline detergents will break down this dealkalized surface and expose the soda-lime compound. Therefore, Type II glass containers may be considered to be of relatively good chemical resistance for only one use.

The glass types are determined from the results of two tests provided by the USP, the Powdered Glass Test and the Water Attack Test. The latter is used only for Type II glass and is performed on the whole container, because of the dealkalized surface. The former test is performed on powdered glass, which exposes internal surfaces of the glass compound. The results are based upon the amount of alkali titrated by 0.02 *N* sulfuric acid after an autoclaving cycle with the glass sample in contact with a high-purity distilled water.

Care must be used in selecting the glass type to be used for a particular injectable product. In general, Type I glass will be suitable for all products, although sulfur dioxide treatment is sometimes used for a further increase in resistance. Because cost must be considered, one of the other less expensive types may be acceptable. Type II glass may be suitable, for example, for a solution which is buffered, has a pH below 7, or is not reactive with the glass. Type III glass will usually be suitable principally for anhydrous liquids or dry substances.

Physical Characteristics—Examples of the physical shape of glass ampuls and vials are illustrated in Fig. 84-3. Commercially available containers vary in size from 0.5 to 1000 ml. Sizes up to 100 ml may be obtained as ampuls and vials, and larger sizes as bottles. The latter are used mostly for intravenous and irrigating solutions. Smaller sizes are also available as cartridges. Ampuls and cartridges are made by being drawn from glass tubing. The smaller size vials, drawn from tubing, have recently become obtainable. The making of tubing is illustrated in Fig. 84-4. Other vials and bottles are made by molding. Containers made by drawing from tubing are generally optically clearer and have a thinner wall than molded containers (see Fig. 84-3). Molded containers are more uniform in external dimensions and are stronger. Therefore, larger containers are made by molding.

Easy-opening ampuls that permit the user to break off the tip of the ampul at the neck constriction without the use of a file are marketed under the names Color-Break (*Kimble*) and Score-Break (*Wheaton*). An example of a modification of container design to meet a particular need is the double-chambered vial, under the name Univial (*Univial*), designed to contain a freeze-dried product in one chamber and solvent in the other. Other examples are wide-mouth ampuls with flat or rounded bottoms to facilitate filling with dry materials

Fig. 84-4. Tubing being formed from molten glass in brick tank (courtesy, Wheaton).

or suspensions, and various modifications of the cartridge for use with disposable dosage units.

Glass containers must be strong enough to withstand the physical shocks of handling and shipping and the pressure differentials that develop, particularly during the autoclave sterilization cycle. They must be able to withstand the thermal shock resulting from striking temperature changes during processing, for example, when the hot bottle and contents are removed from the autoclave at the end of the sterilization cycle. Therefore, a glass having a low coefficient of thermal expansion is necessary. The glass container also must be transparent to permit inspection of the contents. Preparations which are light-sensitive must be protected by placing them in amber glass containers or by enclosing flint glass containers in opaque cartons labeled to remain on the container during the period of use. Silicone coatings are sometimes applied to containers to produce a hydrophobic surface as a means of reducing adherence of a heavy, costly suspension or the friction of a rubber-tip of a syringe plunger.

The size of single-dose containers is limited to 1000 ml by the USP and multiple-dose containers to 30 ml, unless stated otherwise in a particular monograph. Multiple-dose vials are limited in size to reduce the number of punctures for withdrawing doses and the accompanying risk of contamination of the contents. As the name implies, single-dose containers are opened with aseptic care and the contents used at one time. These may range in size from 1000-ml bottles to 1-ml or less ampuls, vials or syringes. The integrity of the container is destroyed when opened so that the container cannot be closed again. A multiple-dose container is designed so that more than one dose can be withdrawn at different times, the container maintaining a seal between uses. It should be evident that with full aseptic precautions, including sterile syringe and needle for withdrawing the dose and disinfection of the exposed surface of the closure, there is still a substantial risk of introducing contaminating microorganisms and viruses into the contents of the vial. Because of this risk, the USP requires that all multiple-dose vials must contain an antibacterial agent. However, there is no effective antiviral agent available for such use. Therefore, in spite of the advantage of flexibility of dosage provided the physician by a multiple-dose vial, the greater safety of single-dose, disposable administration units has caused their use to increase rapidly during recent years.

Rubber Closures

In order to permit introduction of a needle from a hypodermic syringe into a multiple-dose vial and provide for resealing of the vial as soon as the needle is withdrawn, each vial is sealed with a rubber closure held in place by an aluminum band. Fig. 84-5 illustrates how this is done. This principle is also followed for single-dose containers of the cartridge type, except that there is only a single introduction of the needle to make possible the withdrawal or expulsion of the contents.

Rubber closures are composed of several ingredients, the primary ones being natural rubber (latex), a synthetic polymer, or a combination of natural rubber and a synthetic polymer. Other ingredients include a vulcanizing agent, usually sulfur; an accelerator, one of several active organic compounds such as 2-mercaptobenzothiazole; an activator, usually zinc oxide; fillers, such as carbon black or limestone; and various other ingredients such as antioxidants and lubricants. These ingredients are compounded together and then vulcanized in the desired shape, making use of molds under high pressure and temperature. Fig. 84-6 shows the molding of rubber closures.

Rubber closures must have sufficient elasticity to provide a snug fit between the closure and the lip and neck of the vial and must spring back to close the hole made by the needle immediately on withdrawal. They must not be so hard that they are highly resistant to the insertion of the needle, and they must not fragment as the hollow needle passes through them. Ideally, they should be completely nonreactive with the solution and its ingredients and should provide a complete barrier to vapor transfer. These qualities are not perfectly met by any rubber compound now available. It is, therefore, essential to determine the compatibility of the rubber compound with each preparation with which it is to be used.[8] In addition to the physical tests of elasticity, hardness, fragmentation, and vapor transfer, the closures should be exposed

Fig. 84-5. Extended view of sealing components for a multiple-dose vial (courtesy, West).

Fig. 84-6. Removing a sheet of rubber closures from a mol

to the product for prescribed periods of time at designated temperature and humidity conditions. The effect on the product of extractives from the rubber compound or loss of ingredients from the product to the closure should be determined analytically. Physicochemical and toxicological tests for evaluating rubber closures are officially described.

The physical shape of some typical closures may be seen in Fig. 84-5. Most closures have a lip and a protruding flange that extends into the neck of the vial or bottle. Many disk closures are now being used, particularly in the high-speed packaging of antibiotics. Slotted closures are used on freeze-dried products to make it possible to insert the closure part way into the neck of the vial during the drying phase of the cycle. Partial insertion provides protection from contamination while permitting escape of water vapor from the drying product. The plunger type is used to seal one end of a cartridge. At the time of use, the plunger expels the product by a needle inserted through the closure at the distal end of the cartridge.

Special design closures are available for use with large-volume intravenous and irrigating solutions under hospital conditions. The intravenous solution closures often have permanent holes for adapters of administration sets; irrigating solution closures usually are designed for pouring.

Production Facilities

A product having components of the best quality quickly may become totally unacceptable if the environment in which it is processed is contaminated or if the manufacturing procedure is not carried out properly. Therefore, the production facilities and the procedure used in processing the product must meet standards adequate for the task to be accomplished. The nearer these standards approach perfection, the better and safer should be the product.

Arrangement of Area

The production area normally should be divided into five sectional areas: the clean-up area, the preparation area, the aseptic area, the quarantine area, and the finishing or packaging area. All of these areas should be designed and constructed for effective ease of cleaning, efficient operation, attractiveness, and comfort of personnel. The extra requirements for the aseptic area are designed to provide an environment where an injection may be exposed to the environment for brief periods during subdivision from a bulk container to the individual dose containers without becoming contaminated. Contamination of concern includes dust, lint, and microorganisms. Such contaminants are normally found floating in the air, lying on counters and other surfaces, on clothing and body surfaces of personnel, in the exhaled breath of personnel, and deposited on the floor. The design and control of an aseptic area is directed toward so reducing the presence of these contaminants that they are no longer a hazard to aseptic filling. Although the aseptic area must be adjacent to support areas so that an efficient flow of components may be achieved, barriers must be provided to minimize ingress of contaminants to the aseptic area. Such barriers may be sealed partitions, often glass-paneled for greater visibility and light. Another type of barrier is an entrance way through security doors that require passage through an airlock so designed that both doors cannot be opened at the same time. Fig. 84-7 shows an arrangement of an aseptic area modified to provide a service area for the areas of maximum security, the aseptic filling rooms.

Flow Plan—In general, the components for a parenteral product will flow from the stockroom, either: (1) to the preparation room, as for ingredients of the formula, or (2) to the clean-up area, as for containers and equipment. See Fig. 84-8 for a process flow diagram. After proper processing in these areas, the components will flow into the security of the aseptic area for filling of the product in appropriate containers. From there the product will pass into the quarantine area where it will be held until all necessary tests have been performed. If the product is to be sterilized in its final container, the passage normally will be interrupted after the product leaves the aseptic area for subjection to the sterilization process. After the results from all tests are known and the

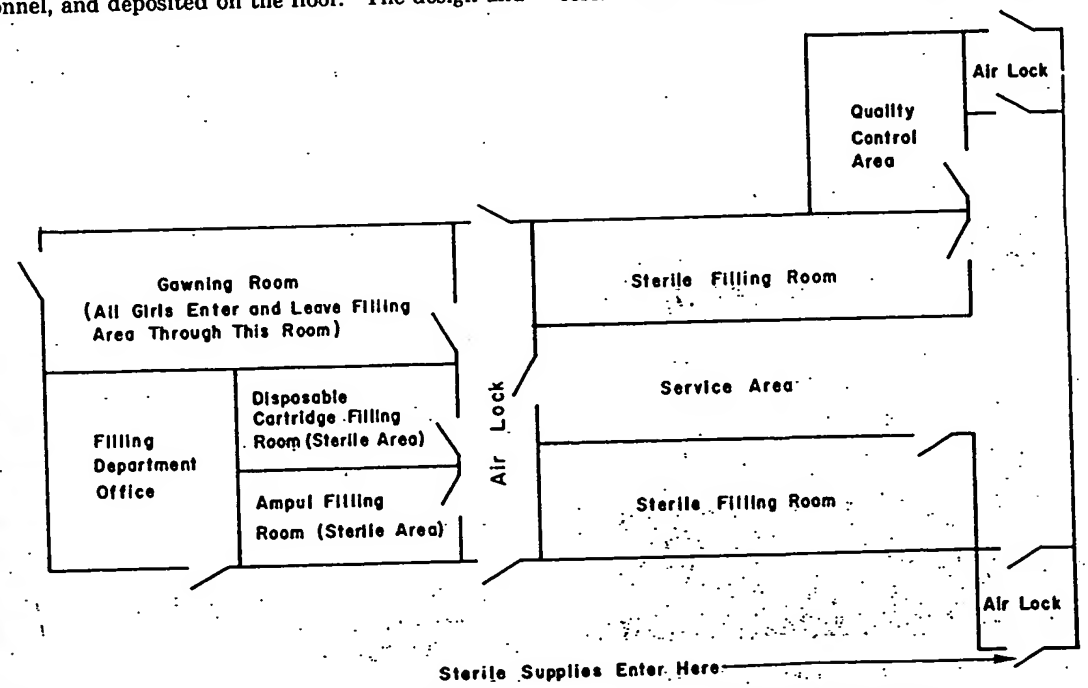

Fig. 84-7. Floor plan of an aseptic filling area with its service area (courtesy, Wyeth).

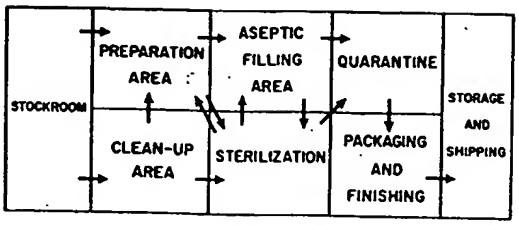

Fig. 84-8. Process flow diagram.

Fig. 84-9. A preparation area adjacent to an aseptic filling area (courtesy, The University of Tennessee College of Pharmacy).

product has been found effective and safe, it will pass to the finishing area for final labeling and packaging. There are sometimes variations from this flow plan to meet the specific needs of an individual product or to conform to available facilities.

Clean-Up Area—The clean-up area will be constructed to withstand moisture, steam, and detergents. The ceiling, walls, and floor should be constructed of impervious materials so that moisture will run off and not be held. These areas should be adequately exhausted so that the heat and humidity will be removed for the comfort of personnel. Precautions must be taken to prevent the accumulation of dirt and the growth of microorganisms, especially in the presence of high humidity and heat. While this area does not need to be aseptic, it must be cleanable and kept clean and the microbial load must be monitored and controlled. Precautions also must be taken to prevent deposit of particles or other contaminants on clean containers and equipment.

Preparation Area—In the preparation area the formula is compounded and preparation is made for the filling operation, such as assembling equipment. Adequate sink and counter space must be provided. Although it is not essential that this area be aseptic, control over it should be more stringent than in the clean-up area. Cabinets and counters should, preferably, be constructed of stainless steel. They should fit snugly to walls and other furniture so that there are no catch areas for dirt to accumulate. Ceiling, walls, and floor should be sealed. One of the "spray-on-tile" finishes with a vinyl or epoxy sealing coat provides a continuous surface free from all holes or crevices. All such surfaces can be washed at regular intervals to keep them thoroughly clean. Fig. 84-9 illustrates such an area.

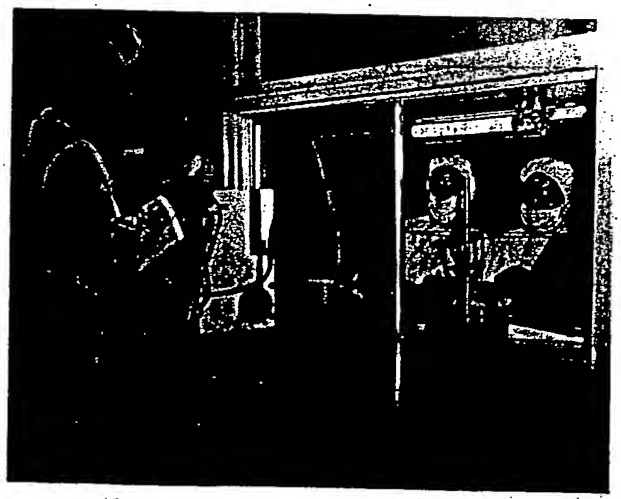

Fig. 84-10. View from service area with pipetting machine and stock bottle retained outside of aseptic filling area (courtesy, Wyeth).

Aseptic Area

The aseptic area requires construction features which have been designed for maximum security. The ceiling, walls, and floor must be sealed so that they not only may be washed but also treated with an antiseptic wipe or spray before each use. All counters should be constructed of stainless steel and hung from the wall so that there are no legs to accumulate dirt where they rest on the floor. All light fixtures, utility service lines, and ventilation fixtures should be recessed in the walls or ceiling to eliminate ledges, joints, and other locations for the accumulation of dust and dirt. As much as possible, tanks containing the compounded product and mechanical equipment should remain outside the aseptic area and the product should be fed into the area through hose lines. Fig. 84-10 shows such an arrangement. Mechanical equipment that must be located in the aseptic area should be housed as completely as possible within a stainless steel cabinet in order to seal the operating parts and their dirt-producing and accumulating tendencies from the aseptic environment. Mechanical parts that will contact the parenteral product should be demountable so that they can be sterilized.

Personnel entering the aseptic area should enter only through an airlock. They should be attired in sterile coveralls with sterile hats, masks, and foot covers. Movement within the room should be minimal and in-and-out movement rigidly restricted during a filling procedure. The requirements for preparation of the room and for the personnel may be relaxed somewhat if the product is to be sterilized in a sealed container. Some are convinced, however, that it is better to have one standard procedure meeting the most rigid requirements.

Air Cleaning

The air in these areas can be one of the greatest sources of contamination. It need not be, however, because several methods are available for providing clean air that is essentially free from dirt particles and microorganisms.

To provide such air, it must be thoroughly cleaned of contaminants. This may be done by a series of treatments. Air from the outside is first passed through a prefilter, usually of glass wool, cloth, or shredded plastic, to remove large particles. Then it is treated by passage through an electrostatic precipitator.* Such a unit induces an electrical charge on particles in the air and removes them by attraction to oppositely charged plates. The air then passes through the most efficient cleaning device, a HEPA (high efficiency partic-

* Suppliers: *Am. Air, Electro-Air, Sturtevant.*

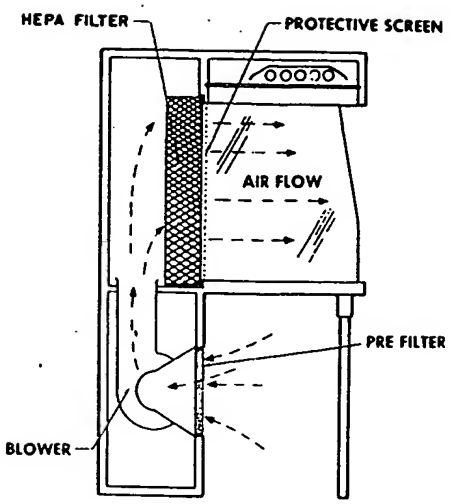

Fig. 84-11. Horizontal laminar flow workbench (courtesy, adaptation, Sandia).

air) filter having an efficiency of at least 99.97% in removing particles of 0.3 μm and larger, based on the DOP test.†

For the comfort of personnel, air conditioning and humidity control should be incorporated into the system. Another available system, the Kathabar system (*Surface Combustion*), cleans the air of dirt and microorganisms by washing it in an antiseptic solution and, at the same time, controls the humidity. The clean, aseptic air is introduced into the aseptic area under positive pressure, which prevents outside air from rushing into the aseptic area through cracks, temporarily open doors, or other openings.

Laminar-Flow Environments—Marked improvement in the environmental control of aseptic areas has been made possible by the development of laminar-flow enclosures. Laminar airflow provides a total sweep of a confined area because the entire body of air moves with uniform velocity along parallel lines, originating through a HEPA filter occupying one entire side of the confined area. Therefore, it bathes the entire area with very clean air, sweeping away contaminants.

The arrangement for the direction of airflow can be horizontal (see Fig. 84-11) or vertical (see Fig. 84-12), and may involve a limited area such as a work bench or an entire room. The effective air velocity is considered to be 100 ± 20 ft/min.

It must be borne in mind that any contamination introduced upstream by equipment, arms of the operator, or leaks in the filter will be blown downstream. In the instance of horizontal flow this may be to the critical working site, the face of the operator, or across the room. Should the contaminant be, for example, penicillin powder or viable microorganisms, the danger is apparent. For operations involving such contaminants a vertical system is much more desirable, with the air flowing through perforations in the counter top or along the edge of the counter where it can be directed for decontamination. Vertical flow has been recommended for sterility-testing procedures.

Laminar-flow environments provide well-controlled work areas only if proper precautions are observed. Any air currents or movements exceeding the velocity of the HEPA-filtered air flow may introduce contamination, as may coughing, reaching, or other manipulations of operators.

Therefore, laminar-flow work areas should be protected by being located within controlled environments. Personnel preferably should be attired for aseptic processing as described above. All movements and processes should be carefully

† Suppliers: *Am. Air, Cambridge, Flanders.*

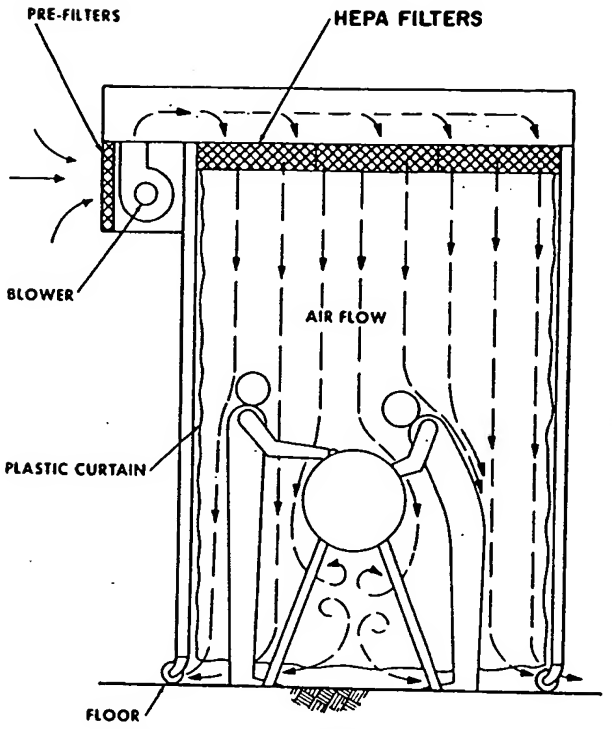

Fig. 84-12. Vertical laminar flow portable room with equipment and operators (courtesy, adaptation, Sandia).

planned to avoid the introduction of contamination upstream of the critical work area. Checks of the air stream should be performed initially and at regular intervals to be sure no leaks have developed through or around the HEPA filters. This can be done most effectively with electronic particle counters.‡

In the manufacture of parenterals, conventional clean room facilities are frequently supplemented by vertical laminar airflow modules suspended above critical sites, such as filling lines. These critical operations are thereby bathed with HEPA-filtered air to provide extra protection for the product.

Laminar flow of HEPA-filtered air should meet the standard for a Class 100 clean room as defined by Federal Standard 209b,[9] which states that such an environment contains no more than 100 particles per cu. ft. of 0.5 μm and larger size. Conventional clean rooms would be of a lesser degree of cleanliness, such as Class 10,000, defined on the same basis. This standard has brought order into defining clean rooms and provided a common basis for their description.

Work benches and other types of laminar-flow enclosures are available from several commercial sources.§

Ultraviolet Radiation

Ultraviolet light rays have an antibacterial action, thereby producing a disinfectant action on directly irradiated surfaces. Since these rays cannot penetrate most materials, only a surface effect is produced, with the principal exception being limited penetration through air and pure water. Ultraviolet light rays travel in straight lines only; therefore, objects in the path of the light beam will cast shadows with a resultant lack of irradiation in the shadow area.

‡ Suppliers: *Air Techniques, Bausch & Lomb, Climet, Dynac, HIAC, Royco.*

§ Suppliers: *Air Control, Atmos-Tech, Baker, BioQuest, Contamination Control, Controlled Environment, DCA, Envirco, Flanders, Laminaire, Liberty, Weber.*

Fig. 84-13. Appropriate uniform for operators entering aseptic filling room (courtesy, Abbott).

Ultraviolet rays are irritating to the skin and, particularly, the eyes of human beings. Therefore, personnel in the area of irradiation must be protected from direct exposure.

Ultraviolet lamps may be installed so as to provide either direct or indirect radiation. Direct irradiation of a room when personnel are not present is a valuable means of reducing bacterial count on working surfaces and floors. Lamps installed above head level, so that personnel present would not be irradiated, can irradiate circulating air to reduce the microbial level continuously during processing.

Local irradiation may be useful in hood-type fixtures, over filling and other process operations, within large storage tanks, or in any place where additional protection from contamination is needed, provided any product present is not adversely affected by ultraviolet rays. Ultraviolet lamps usually are not employed in conjunction with laminar-flow facilities because the HEPA-filtered air sweeps exposed surfaces clean and because the air itself flows too fast for adequate lethal irradiation of microorganisms being carried in the air stream.

It must be stated that although bacteria may be killed by irradiation with ultraviolet light for a sufficient time at an effective intensity, it has been found that certain bacteria have grown after exposure to supposedly lethal irradiation. This attenuating rather than killing effect was found by subjecting the organisms to certain conditions after irradiation, such as special nutrients, change in pH, darkness, and daylight.

The best practical source of ultraviolet light rays is the cold-cathode mercury vapor lamp. This lamp emits a high proportion of ultraviolet rays at the 253.7 nm wavelength. A special glass is used for the tube so that the rays will pass to the outside. This glass will gradually change in crystal structure with use so that passage of the rays is gradually reduced. Such lamps, therefore, rarely burn out as do visible light lamps but gradually reach an emission level which is ineffective. These lamps also must be kept clean, for dust and grease will drastically lower the effective emission. It is generally stated that an irradiation intensity of 20 $\mu w/cm^2$ is required for effective antibacterial activity.

Maintenance of the Aseptic Area

One of the most important aspects in the control of environmental contamination in the aseptic area is the care and maintenance. This work should not be done in a haphazard manner by the general maintenance crews, but rather by crews given special instruction and under the supervision of personnel trained in the care of aseptic areas. In general, the cleaning and maintenance should be done after the completion of the day's work with an interval of quietude before the beginning of another aseptic operation. All maintenance equipment should be selected for its effectiveness and freedom from lint-producing tendencies and should be reserved for use in the aseptic areas only.

Personnel

Personnel selected to work on the preparation of a parenteral product must be neat, orderly, and reliable. They should be in good health and free from dermatological conditions that might increase the microbial load. If they show symptoms of a head cold or other illness, they should not be permitted in the aseptic area until recovery is complete. They must receive intensive instruction in the principles of aseptic processes. They also must be made to appreciate the vital part that every movement they make has in determining the reliability of the final product. Supervisors should be selected with particular care. They must be individuals who understand the particular requirements of aseptic procedures and who are able to obtain the full participation of other employees in fulfilling these exacting requirements.

The attire prescribed for personnel varies from one manufacturing facility to another. However, uniforms should be freshly laundered for each day. For use in the aseptic area, it is generally agreed that uniforms should be sterile. This means that fresh, sterile uniforms should be used after every break period, or whenever the individual returns to the aseptic area. In some plants this is not required if the product is to be sterilized in its final container. The uniform usually consists of coveralls for both men and women, hoods to completely cover the hair, face masks, and cloth or plastic boots (Fig. 84-13). Sterile rubber gloves also may be required for most aseptic operations, preceded by thorough scrubbing of the hands with a disinfectant soap. The uniform is designed to confine the contaminants discharged from the body of the operator, thereby preventing their ingress into the product.

Lint is also a problem in these areas. Although cotton uniforms are usually more comfortable, Dacron uniforms are essentially lint-free and are reasonably comfortable. Air showers are sometimes directed on personnel entering the processing area to blow loose lint from the uniforms.

Environmental Control Tests

In spite of the elaborate precautions taken by pharmaceutical manufacturers to provide satisfactory conditions for the proper processing of parenterals, the air may become laden with bacteria or other particles with subsequent contamination of the product. To monitor this condition suitable environmental control tests should be performed at regular intervals.

One air-sampling technique employed involves the collection of particulate matter from the air by drawing a sample of the air through a clean, sterile membrane filter of bacteria-retentive porosity. The filter is placed in a holder* designed to hold the filter flat and to prevent leakage. An accurately measured, predetermined volume of air is drawn through it

* Suppliers: *Gelman, Millipore, Nuclepore, Sartorius.*

filter. Planned locations for sampling should be chosen to reveal potential contamination levels at such places as the filling and sealing area, beside personnel, next to moving equipment, and near doorways or other openings. A new filter should be used at each location. The filters then may be examined microscopically for particulate matter, such as lint and dust, or placed on culture media and incubated for the detection of microorganisms.

To eliminate the dehydrating effect on microorganisms, the air sample may be drawn into a measured volume of nutrient broth in an impinger. Organisms in the broth then may be collected by filtration on a membrane filter and incubated. In order to be meaningful, such a test must be conducted at planned intervals, with standards set from experience to decide the level of contamination permissible.

Another microbiological air-sampling technique consists of drawing a measured volume of air through a narrow opening which causes the air to impinge on the surface of a rotating nutrient agar plate, a slit sampler. This provides a measurement of the number of organisms at a given time during the sampling period. A cascade sampler relates the number of organisms in the air sample to size. It consists of a series of perforated plates located over nutrient agar plates, the perforations in the plates decreasing in size downstream. Larger dust particles carrying bacteria or aggregates of bacteria are collected on the surface of the upper plates and smaller particles on the surface of the lower plates.

Probably the most widely used method involves the exposure of nutrient agar culture plates to the settling of microorganisms from the air. If pathogenic microorganisms are particularly of interest, blood agar plates may be needed. With this method also, the locations for the collection of the samples should be planned carefully. The exposure period should be planned and should be uniform each time in order that comparisons may be meaningful. The exposure period may vary as deemed needful for given circumstances, but even a period of one hour may not collect one microorganism under conditions of use in a well-controlled aseptic area.

Samples of the level of microorganisms on surfaces can be determined with specially designed nutrient agar plates having a convex surface (Rodac Plates). With these plates it is possible to roll the raised agar surface over flat or irregular surfaces to be tested. Organisms will be picked up on the agar and will grow during subsequent incubation.

Results from these tests are very valuable to keep cleaning, production, and quality control personnel apprised of the level of contamination in a given area. The results may also serve to detect environmental control defects such as failure in air-cleaning equipment or the presence of personnel who may be disseminating large numbers of bacteria without apparent physical ill effects.

Another test which is much more stringent is to fill and seal sterile fluid thioglycollate medium or trypticase soy broth in sterile containers under the same conditions used for an aseptic fill of a product. The entire lot is then incubated and examined subsequently for the appearance of growth of microorganisms. Such growth is indicative of contamination from the environment, including the equipment. It also may be used as a measure of the efficiency of a particular operator. Since this is a total sterility test, it is the best indication of the efficiency of the aseptic filling process.

Several instrumental methods are currently being utilized to obtain particle counts from a measured volume of air as a means of indicating the level of particle contamination in the environment. These instruments operate on the principle of the measurement of light scattered from particles passed through the optical system.† They can be adjusted to measure particles of a broad or narrow range of particle size. Difficulty has been experienced in obtaining consistent results, but their automatic features and immediate results make them useful for routine monitoring of an environment.

† Suppliers: *ATI, Bausch & Lomb, Climet, Dynac, HIAC, Particle Tech., Royco.*

Production Procedures

Cleaning Containers and Equipment

Containers and equipment coming in contact with parenteral preparations must be meticulously cleaned. It is obvious that if this were not so, all other precautions to prevent contamination of the product would be useless. It also should be obvious that even new, unused containers and equipment will be contaminated with such debris as dust, fibers, chemical films, and other materials arising from such sources as the atmosphere, cartons, the manufacturing process, and human hands. Much greater contamination must be removed from previously used containers and equipment before they will be suitable for reuse. Equipment should be rigidly reserved for use only with parenteral preparations and, where conditions dictate, only for one type product in order to reduce the risk of contamination.

A variety of machines are available for the cleaning of containers for parenteral products. These vary in complexity from a single jet tube for rinsing by hand one inverted container at a time with distilled water, to complex, automatic washers capable of processing several thousand containers an hour. The selection of the particular type to be used will be determined largely by the physical type of containers, their condition with respect to contamination, and the number of containers to be processed in a given period of time.

Characteristics of Machinery—Regardless of the type of cleaning machine selected, certain fundamental characteristics are usually required.

1. The liquid or air treatment must be introduced in such a manner that it will strike the bottom of the inside of the inverted container, spread in all directions, and smoothly flow down the walls and out the opening with a sweeping action. The pressure of the jet stream should be such that there is minimal splashing, and the flow should be such that it can leave the container opening without accumulating and producing turbulence inside. Splashing may prevent cleaning all areas and turbulence may redeposit loosened debris. Therefore, direct introduction of the jet stream within the container with control of the flow of the jet stream is required.
2. The container must receive a concurrent outside rinse.
3. The cycle of treatment should provide for a planned sequence with alternation of very hot and cool treatments. The final treatment should be an effective rinse with water of a quality equivalent to Water for Injection.
4. All metal parts coming in contact with the containers and with the treatments should be constructed of stainless steel or some other noncorroding and noncontaminating material.

Treatment Cycle—The cycle of treatments to be employed will vary with the condition of the containers to be cleaned. In general, loose dirt can be removed by vigorous rinsing with water. Detergents are rarely used for new containers because of the risk of leaving detergent residues. However, a thermal-shock sequence in the cycle is usually

Fig. 84-14. Rotary rinser in clean environment provided by vertical laminar air flow within curtained enclosure (courtesy, Ciba-Geigy).

Fig. 84-15. Conveyor rinser discharging clean vials in preparation area (courtesy, Schering).

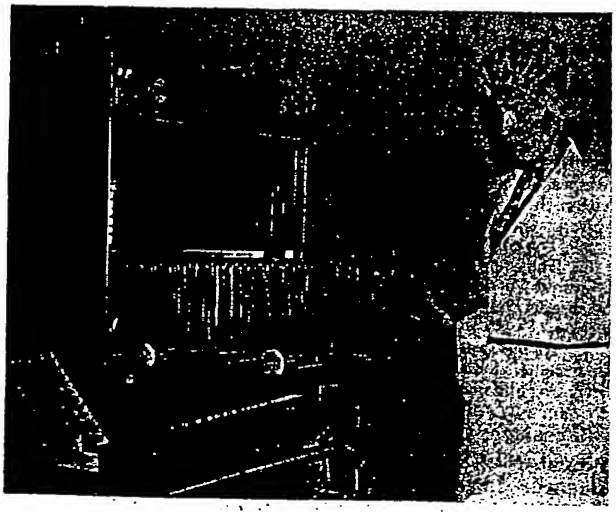

Fig. 84-16. Cabinet washer being loaded with ampuls (courtesy, The University of Tennessee College of Pharmacy).

employed to aid, by expansion and contraction, loosening of debris that may be adhering to the container wall. Sometimes only an air rinse is used for new containers, particularly if used for a dry powder. In all instances the final rinse, whether air or Water for Injection, must be ultraclean so that no particulate residues are left by the rinsing agent.

Containers previously used cannot be reliably cleaned and the cost of attempting to do so is prohibitive. Therefore, normally, only new containers are used for parenterals. Improvements have been made in maintaining their cleanliness during shipment from the manufacturer through tighter, low-shedding packaging, including plastic blister packs.

Machinery for Containers—The machinery available for cleaning large numbers of containers embodies the above principles but varies in the mechanics by which it is accomplished. In one approach, the jet tubes are arranged on arms like the spokes of a wheel, which rotate around a center post through which the treatments are introduced. An operator places the unclean containers on the jet tubes as they pass the loading point and removes the clean containers as they complete one rotation. Such a machine is pictured in Fig. 84-14. Another machine has a row of jet tubes across a conveyor belt. The belt moves the row of containers past the treatment stations and discharges the clean containers on the opposite end of the machine, preferably through a wall into a clean room. Two operators are required for this machine (Fig. 84-15). A cabinet-type washer permits loading the containers on a rack of jet tubes. The rack is pushed inside the cabinet during the cleaning cycle. This type of machine permits handling a variety of sizes and types of containers quite easily, but the number of containers handled in a given period of time is relatively small. Fig. 84-16 shows a machine of this type. A machine designed to process a large number of containers, particularly bottles and larger size containers, employs a conveyor chain to draw rows of jet tubes through a long tunnel where the treatments are introduced. The clean containers are returned to the loading point for removal (*Better Built*).

The disadvantage common to all of the above types of machines is said that they require the individual handling of each container for loading and unloading. A type which overcomes this disadvantage is the rack-loading washer. Racks are prepared to fit over the open ends of ampuls or vials as they are found in shipping cartons. Inverting the carton permits the containers to be transferred from the carton to the washer without handling the individual containers. A battery of jet tubes is arranged to enter each container positioned in the rack. The clean containers may be removed in the rack and transferred to a box for dry-heat sterilization and storage (see Fig. 84-17). More details of the industrial washing of glassware have been given by Anschel.[10]

Handling after Cleaning—The wet, clean containers must be handled in such a way that contamination will not be reintroduced. A wet surface will much more readily collect contaminants than will a dry surface. For this reason wet rinsed containers should be protected, such as by a laminar flow of clean air until covered, as within a stainless steel box. (See Figs. 84-14 and 84-18.) In addition, microorganisms are more likely to grow in the presence of moisture. Therefore it is preferable, if not required, that containers be dry-heat sterilized in a stainless steel box that will protect the containers from contamination during storage after sterilization. Doubling the heating period will also assure destruction of pyrogens, especially likely to be present on reused containers. If it is proved that sterilization is not essential, the containers should be filled immediately with product or dried and stored where they will be protected from contamination until used. Immediate filling eliminates the need for storage of the clean containers, but it also eliminates the sterilizing and depyrogenating step of the dry-heat treatment, often a vital step.

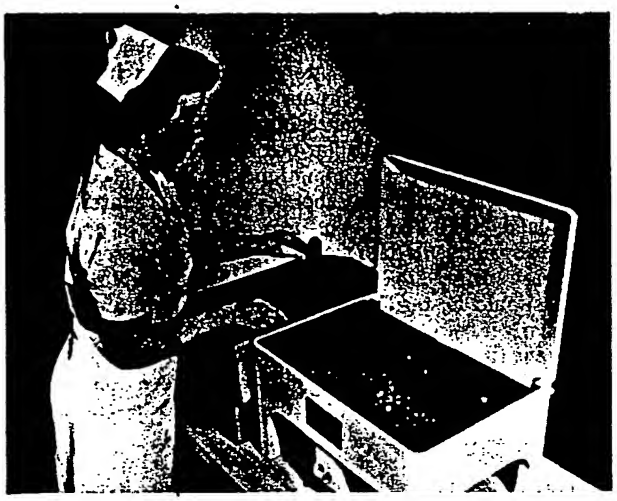

Fig. 84-17. Metromatic rack-loader washer being loaded directly from container carton (courtesy, Price).

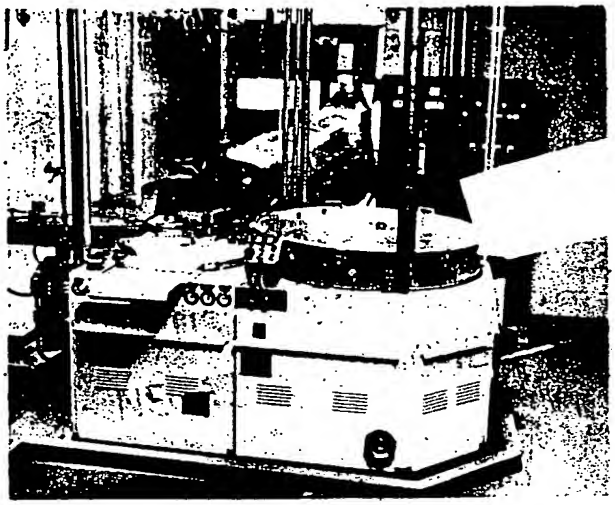

Fig. 84-18. Continuous automatic line operation for vials from rotary rinser through sterilizing tunnel with vertical laminar air flow protection of clean vials (courtesy, Abbott).

Therefore, it should be used only where a sterile pyrogen-free container is not essential.

Increases in process rates have necessitated the development of continuous-line processing with a minimum of individual handling, still maintaining adequate control of the cleaning and handling of the containers. Fig. 84-18 shows a continuous automatic-line operation from feeding the unwashed container into the rotary rinser to passage through the drying and sterilizing tunnel. The clean, wet containers are protected by filtered laminar-flow air from the rinser through the tunnel and are then delivered to the filling line.

Closures—Rubber closures are coated with lubricant from the molding operation. In addition, the rough surface and electrostatic attraction tend to hold debris. Also, the surface "bloom" from migrated inorganic constituents of the compound must be removed. The recommended procedure calls for gentle agitation in a hot solution of a water softener such as 0.5% sodium pyrophosphate. The closures are removed from the solution and rinsed several times with water and finally with filtered distilled water. The rinsing is to be done in a manner which will flush away loosened debris. The closures are then usually sterilized by autoclaving in Water for Injection and stored in closed containers until ready for use. At times this step is carried out in a solution of the bacteriostatic agent to be used in the product, in order to equilibrate the rubber closure with the agent. Subsequent loss of the agent from the solution to the closure is then less likely to occur. To reduce hydration of the rubber compound, the Water for Injection or solution in which the closures were immersed during autoclaving is drained off before storage. If the closures must be dry for use, they may be subjected to vacuum drying at a temperature in the vicinity of 100°C.

The equipment used for washing large numbers of closures is usually an agitator or horizontal basket-type automatic washing machine. Because of particulate generation from the abrading action of these machines, some heat the closures in kettles in detergent solution and follow with prolonged flush rinsing. The final rinse always should be ultraclean Water for Injection.

Equipment—Details of certain prescribed techniques for the cleaning and preparation of equipment, as well as of containers and closures, have been presented elsewhere.[11] Here, a few points will be emphasized.

All equipment should be disassembled as much as possible to provide access to internal structures. All parts should be scrubbed thoroughly with a stiff brush using an effective detergent, paying particular attention to joints, crevices, screw threads, and other structures where debris is apt to collect. Exposure to a stream of clean steam will aid in dislodging residues from the walls of stationary tanks, spigots, pipes, and similar structures. Thorough rinsing with distilled water should follow the cleaning steps. Large stationary tanks, such as those shown in Fig. 84-19, should be protected as much as possible from contamination after cleaning but should be rinsed thoroughly again with distilled water prior to reuse.

Sometimes dichromate cleaning solution is used on glassware. While this solution will effectively clean glassware of traces of organic residues, it should be used cautiously since the dichromate ion adheres strongly to the glass surface and is completely removed only with great difficulty. Should any remain, it may be transferred to the product subsequently made in the glassware and produce detrimental effects.

Rubber tubing, rubber gaskets, and other rubber parts may be washed in a manner such as described for rubber closures. Thorough rinsing of tubing must be done by passing distilled water through it. If more rigorous treatment is required for new tubing or parts, it has been suggested that the tubing should be soaked in 10% sodium hydroxide solution for 24 hours, rinsed thoroughly, boiled for 1 hour in 1% hydrochloric acid solution, and rinsed thoroughly with distilled water.

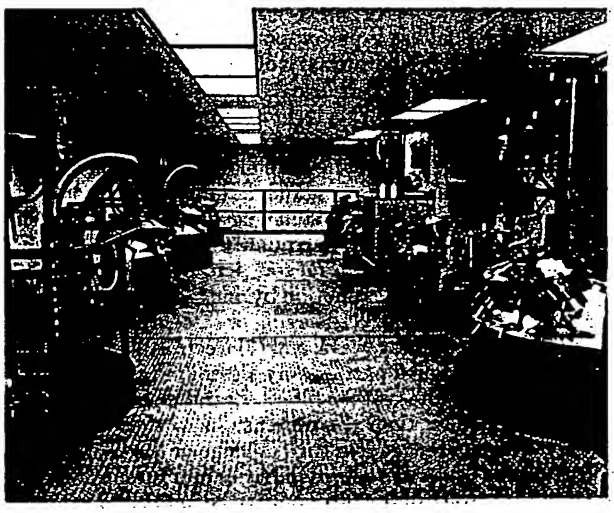

Fig. 84-19. Large stainless steel tanks for product preparation showing mezzanine level for access (courtesy, Abbott).

Rubber tubing must be left damp when preparing for sterilization by autoclaving.

Product Preparation

The basic principles employed in the compounding of the product do not vary from those used routinely by qualified pharmacists. However, selected aspects will be mentioned for emphasis. All measurements should be made as accurately as possible and should be checked by a second qualified person. Although most liquid preparations are made by volume, where possible they should be made by weight, with the weight experimentally determined from the required volume. This method is more accurate since no consideration need be given to the temperature of the components. In addition, measurements by weight normally can be performed more accurately than those by volume.

Care must be taken that equipment is not wet enough to significantly dilute the product or, in the case of anhydrous products, to cause a physical incompatibility. The order of mixing of ingredients may significantly affect the product, particularly those of large volume where attaining homogeneity requires considerable mixing time. For example, adjustment of pH by addition of a dilute acid may cause excessive local reduction in the pH of the product so that adverse effects are produced before the acid can be dispersed throughout the entire volume of product.

Parenteral dispersions, including colloids, emulsions, and suspensions, provide particular problems. These have been reviewed by Macek[12] and by Nash.[13] In addition to the problems of achieving and maintaining proper reduction in particle size under aseptic conditions, the dispersion must be kept in a uniform state of suspension throughout preparative, transfer, and subdividing operations.

The formulation of a stable product is of paramount importance. Certain aspects of this have been mentioned in the discussion of components of the product. Exhaustive coverage of the topic is not possible within the limits of this text, but further coverage is provided in Chapter 75. It should be mentioned here, however, that thermal sterilization of parenteral products increases the possibility of chemical reactions. Such reactions may progress to completion during the period of elevated temperature in the autoclave, or be initiated at this time but continue during subsequent storage. Assurance of attainment of stability in a product requires a high order of pharmaceutical knowledge and responsibility.

Filtration

After a product has been compounded, if it is a solution it must be filtered. The primary objective of filtration is to clarify a solution. A high degree of clarification is termed "polishing" a solution. This term is applied when particulate matter down to approximately 2 μm in size is removed. A further step, removing particulate matter down to 0.2 μm in size, would eliminate microorganisms and would accomplish "cold" sterilization. A solution having a high degree of clarity conveys the impression of high quality and purity, desirable characteristics for a parenteral solution.

Filters are thought to function by one or, usually, a combination of the following: (1) sieving or screening, (2) entrapment in tortuous passageways, and (3) electrostatic attraction. When a filter retains particles by sieving, the particles are retained on the surface of the filter. Entrapment occurs when a particle, smaller than the dimensions of the passageway (pore), becomes lodged in a turn or ledge of the passageway. Electrostatic attraction causes particles opposite in charge to that of the surface of the filter pore to be held or adsorbed to the surface. It should be noted that increasing or prolonging the force behind the solution may tend to sweep particles held by entrapment or electrostatic charge through the pores and into the filtrate.

Today, membrane filters are used almost exclusively for filtration of parenteral solutions. Their particle retention effectiveness, flow rate, nonreactivity and disposable characteristics have justified their use to the exclusion of most other types. The most common membranes are composed of cellulose ester* or polycarbonate† but other materials are being used, including Teflon and other plastic polymers. They are available as flat membranes or pleated into cylinders to increase surface area and, thus, flow rate. Each filter in its holder should be tested for integrity before and after use, particularly if being used to eliminate microorganisms. While membrane filters are disposable, and thus discarded after use, the holders must be thoroughly cleaned between uses. Other characteristics of these filters, important for a full understanding of their use, are given in Chapter 78.

Filling

During the filling of containers with a product, the most stringent requirements must be exercised to prevent contamination, particularly if the product has been sterilized by filtration and will not be sterilized in the final container. Under the latter conditions it is usually called an "aseptic fill." During the filling operation, the product must be transferred from a bulk container and subdivided into dose containers. This operation exposes the product to the environment, equipment, and manipulative technique of the operator until it can be sealed in the dose container. Therefore, this operation is carried out in the aseptic filling area where maximum protection is provided. Additional protection may be provided by filling under a blanket of HEPA-filtered laminar-flow air within the aseptic area.

Normally, the compounded product is in the form of either a liquid or a solid. A liquid is more readily subdivided uniformly and introduced into a container having a narrow mouth than is a solid. Mobile, nonsticking liquids are considerably easier to transfer and subdivide than viscous, sticky liquids. The latter require heavy-duty machinery for rapid production filling.

Although many devices are available for filling containers with liquids, certain characteristics are fundamental to them all. A means is provided for repetitively forcing a measured volume of the liquid through the orifice of a delivery tube which is introduced into the container. The size of the delivery tube will vary from that of about a 20-gauge hypodermic needle to a tube 1 in. or more in diameter. The size required is determined by the physical characteristics of the liquid, the speed of delivery desired, and the inside diameter of the neck of the container. The tube must enter the neck of the container and deliver the liquid well into the neck to eliminate spillage, allowing sufficient clearance to permit air to leave the container as the liquid enters. The delivery tube should be as large as possible in diameter in order to reduce the resistance to the flow of the liquid. For smaller volumes of liquids the delivery is usually obtained from the stroke of the plunger of a syringe, forcing the liquid through a two-way valve providing for alternate filling of the syringe and delivery of mobile liquids. A sliding piston valve would be used for heavy, viscous liquids. For large volumes the quantity delivered is usually measured in the container by the level of fill in the container, the force required to transfer the liquid being provided by gravity, a pressure pump, or a vacuum pump.

The narrow neck of an ampul limits the clearance possible between the delivery tube and the inside of the neck. Sin

* Suppliers: *Gelman, Millipore, Sartorius, Schleicher.*
† Supplier: *Nuclepore.*

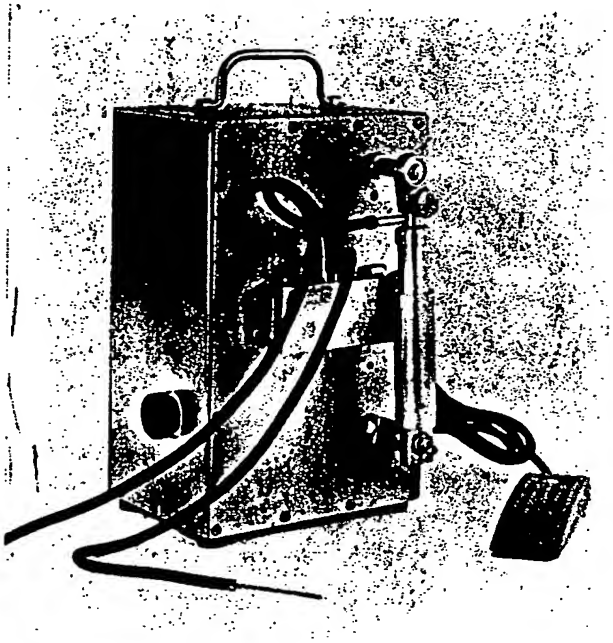

Fig. 84-20. Filling machine employing piston valve and stainless steel syringe (courtesy, Chase-Logeman).

a drop of liquid normally hangs at the tip of the delivery tube after a delivery, the neck of an ampul will be wet as the delivery tube is withdrawn, unless the drop is retracted. Therefore, filling machines should have a mechanism by which this drop can be drawn back into the lumen of the tube.

Since the liquid will be in intimate contact with the parts of the machine through which it flows, these parts must be constructed of nonreactive materials such as borosilicate glass or stainless steel. In addition, these parts should be easily demountable for cleaning and for sterilization.

Because of the increased concern for particulate matter in injectable preparations, a final filter is often inserted in the system between the filler and the delivery tube. Most frequently this is a membrane filter, having a porosity of approximately 1 μm and treated to have a hydrophobic edge. The latter is necessary to reduce the risk of rupture of the membrane due to filling pulsations. It should be noted that the insertion of the filter at this point should collect all particulate matter generated during the process, only that which may be found in inadequately cleaned containers or picked up from exposure to the environment after passage through the final filter potentially remaining as contaminants. However, the filter does cushion liquid flow and reduces the efficiency of drop retraction from the end of the delivery tube, sometimes making it difficult to control delivery volume as precisely as would be possible without the filter.

Liquids—The filling of a small number of containers may be accomplished with a hypodermic syringe and needle, the liquid being drawn into the syringe and forced through the needle into the container. A device for providing greater speed of filling is the Cornwall Pipet (*BD & Co.*). This device has a two-way valve between the syringe and the needle and a means for setting the stroke of the syringe so that the same volume will be delivered each time.

Mechanically operated instruments substitute a motor for the operator's hand in the previous devices described. Thereby, a much faster filling rate can be achieved. By careful engineering, the stroke of the syringe can be repeated precisely; and so, once a particular setting has been calibrated to the delivery, high delivery precision is possible. However, the speed of delivery, the expansion of rubber tubing connecting the valve with the delivery tube, and the rapidity of action of the valves can affect the precision of delivery. A filling machine employing a two-way valve assembly is shown in operation in Fig. 84-10. One employing a piston valve is shown in Fig. 84-20. Stainless steel syringes are usually employed with viscous liquids because glass syringes are not strong enough to withstand the high pressures developed during delivery.

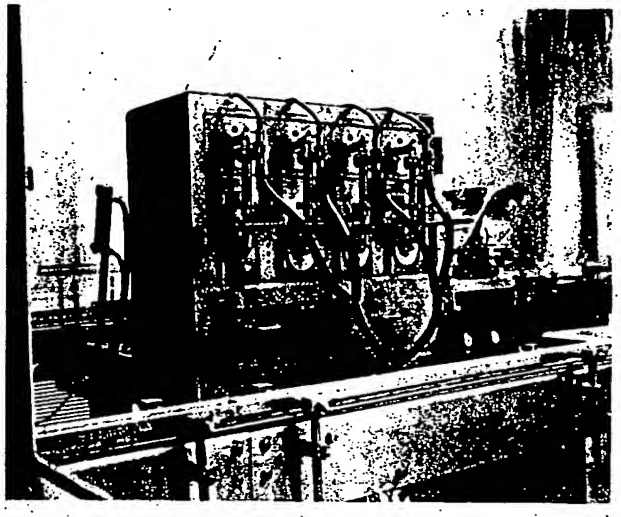

Fig. 84-21. Four-pump liquid filler, with conveyor line for vials protected by vertical laminar air flow and plastic curtain; note automatic stoppering machine on right within curtain (courtesy, Abbott).

When high-speed filling rates are desired but accuracy and precision must be maintained, multiple filling units are often joined together in an electronically coordinated machine, such as shown in Fig. 84-21.

Fig. 84-22 illustrates the filling of large-volume bottles by means of a pressure pump filler. As the delivery tube is lowered into the bottle, the rubber sealer is pressed against the lip of the bottle and the pressure opens a pinch valve. This permits the liquid to flow into the container until it reaches the overflow tube. The operator then raises the delivery assembly, automatically closing the pinch valve. The level of fill is governed by the position of the overflow tube in the container. Any liquid drawn into the overflow tube is returned to the reservoir. It is obvious that the accuracy of fill will vary since it is determined by the height of the liquid in the bottle. It is customary to plan a liberal excess with such filling operations.

Most high-speed fillers for larger volume solutions also utilize the bottle as the measuring device, transferring the liquid either by vacuum or positive pressure from the bulk reservoir to the individual unit containers. Therefore, a high accuracy of fill is not achievable.

The USP indicates that each container should be filled with a slight excess of volume and gives a table of such suggested excess.

Solids—Sterile solids, such as antibiotics, are more difficult to subdivide evenly into containers than are liquids. The rate of flow of solid material is slow and irregular. Even though a container with a larger diameter opening is used to facilitate filling, it is difficult to introduce the solid particles, and the risk of spillage is ever present. The accuracy of the quantity delivered cannot be controlled as well as with liquids. Because of these factors, the tolerances permitted for the content of such containers must be relatively large. Suggested tolerances will be found in the USP.

Some sterile solids are subdivided into containers by individual weighing. A scoop is usually provided to aid in approximating the quantity required, but the quantity filled into

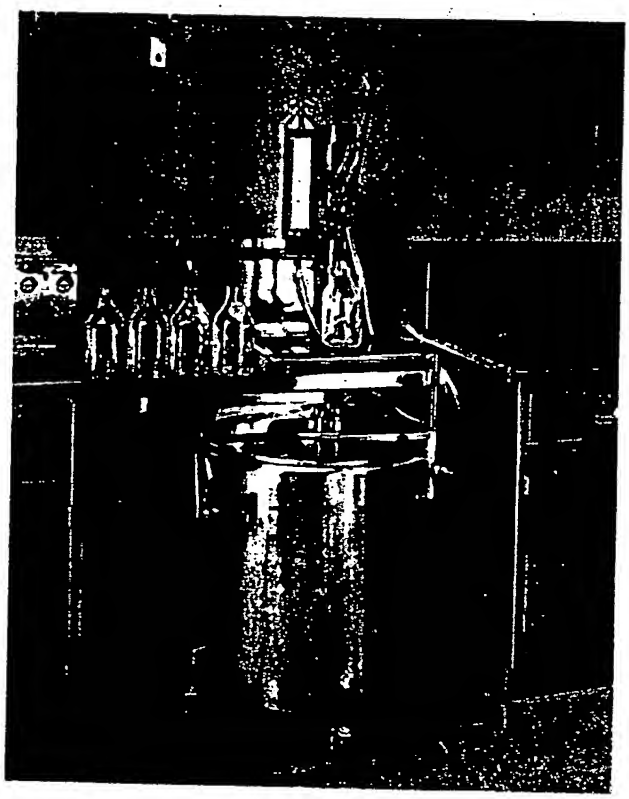

Fig. 84-22. A pressure pump filler for liter solution bottles in a hospital (courtesy, Am. Sterilizer).

the container is finally weighed on a balance. This is a slow process. When the solid is obtainable in a granular form so that it will flow more freely, other methods of filling may be employed. In general, these methods involve the measurement and delivery of a volume of the granular material which has been calibrated in terms of the weight desired. In a machine, shown in Fig. 84-23, an adjustable cavity in the rim of a wheel is filled by vacuum and the contents held by vacuum until the cavity is inverted over the container. The solid material is then discharged into the container by the use of sterile air. Another machine employs an auger in the stem of a funnel at the bottom of a hopper. The granular material is placed in the hopper. By controlling the size of the auger and its rotation, a regulated volume of granular material can be delivered from the funnel stem into the container. Such a machine is shown in Fig. 84-24.

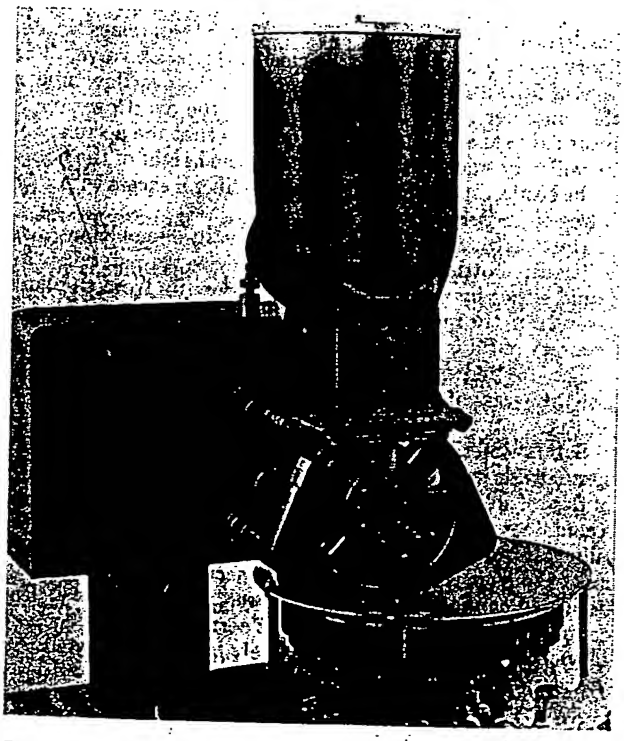

Fig. 84-23. Accofil vacuum powder filler (courtesy, Perry).

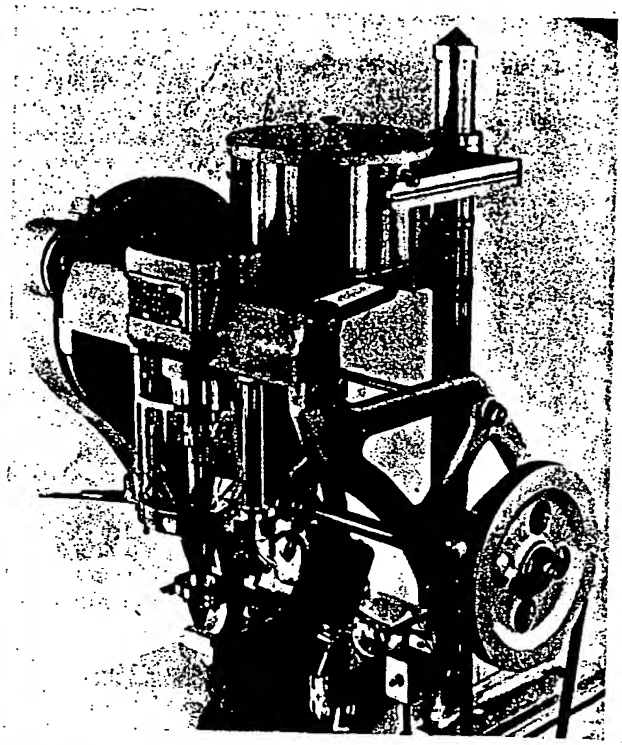

Fig. 84-24. Auger-type powder filler (courtesy, Chase-Logeman).

Sealing

Ampuls—Filled containers should be sealed as soon as possible to prevent the contents from being contaminated by the environment. Ampuls are sealed by melting a portion of the glass neck. Two types of seals are normally employed, either tip-seals (bead-seals) or pull-seals. Tip-seals are made by melting enough glass at the tip of the neck of an ampul to form a bead and close the opening. Such seals can be made rapidly in a high-temperature gas–oxygen flame. To produce a uniform bead, the ampul neck must be heated evenly on all sides. This may be accomplished by means of burners on opposite sides of stationary ampuls (see Fig. 84-25) or by rotating the ampul in a single flame. Care must be taken to properly adjust the flame temperature and the interval of heating to obtain complete closing of the opening with a bead of glass. Excessive heating will result in expansion of gas within the ampul against the soft bead seal and cause a bubble to form. If the bubble bursts, the ampul is no longer sealed; if it does not, the wall of the bubble will be thin and fragile. Insufficient heating will leave an open capillary through the center of the bead. An incompletely sealed ampul is called a "leaker."

Pull-seals are made by heating the neck of the ampul below the tip, leaving enough of the tip for grasping with forceps or other mechanical devices. The ampul is rotated in the flame from a single burner. When the glass has softened, the tip is grasped firmly and pulled quickly away from the body of the

Fig. 84-25. Ampuls being sealed in a crossfire of a Bunsen burner (courtesy, Hynson).

ampul, which continues to rotate. The small capillary tube thus formed is twisted closed. Pull-sealing is slower, but the seals are more sure than tip-sealing. Fig. 84-26 shows a machine combining the steps of filling and pull-sealing ampuls.

Powder ampuls or other types having a wide opening must be sealed by pull-sealing. Were these ampuls sealed by bead-sealing, the very large bead produced would induce glass strain with subsequent fracture at the juncture of the bead and neck wall. Fracture of the neck of ampuls during sealing also may occur if wetting of the necks occurred at the time of filling. Also, wet necks increase the frequency of bubble formation. If the product in the ampul is organic in nature, wet necks will also result in unsightly carbon deposits from the heat of sealing.

In order to prevent decomposition of a product, it is sometimes necessary to displace the air in the space above the product in the ampul with an inert gas. This is done by introducing a stream of the gas, such as nitrogen or carbon dioxide, during or after filling with the product. Immediately thereafter the ampul is sealed before the gas can diffuse to the outside.

Vials and Bottles—These are sealed by closing the opening with a rubber closure (stopper). This must be accomplished as rapidly as possible after filling and with reasoned care to prevent contamination of the contents. The large opening makes the introduction of contamination much easier than with ampuls. Therefore, a means should be provided to keep these containers covered except for the few seconds required for filling and for the actual introduction of the rubber closure. In Fig. 84-21 the automatic conveyorized procedure is being performed under vertical laminar air flow within plastic side curtains.

The closure must fit the mouth of the container snugly enough so that its elasticity will permit adjustment to slight irregularities in the lip and neck of the container. However, it must not fit so snugly that it is difficult to introduce into the neck of the container. When rubber closures are to be inserted mechanically, the surface of the closure is often halogenated to give it less friction. Thus, it is possible to convey the closure through a shute to the place where it is positioned over a vial and then inserted by a plunger or some other pressure device. Mechanical stoppering has been developed in recent years because of the need for high-speed production. An example of such a mechanical device is shown in Fig. 84-27. Closures may also be inserted aseptically with sterile forceps or directly with hands encased in sterile rubber gloves. In a modification of this technique, rubber closures may be picked up and then inserted into a vial by means of a tool connected to a vacuum line.

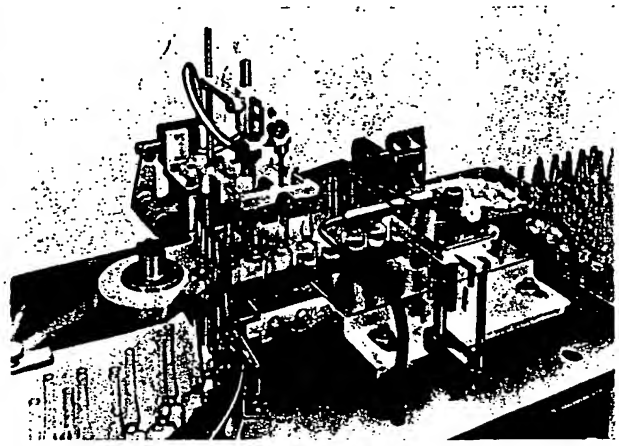

Fig. 84-26. Automatic filling and pull-sealing of ampuls (courtesy, Cozzoli).

Rubber closures are held in place by means of aluminum caps. The aluminum cap covers the closure and is crimped under the lip of the vial or bottle to hold the closure in place (see Fig. 84-5). The closure cannot be removed without de-

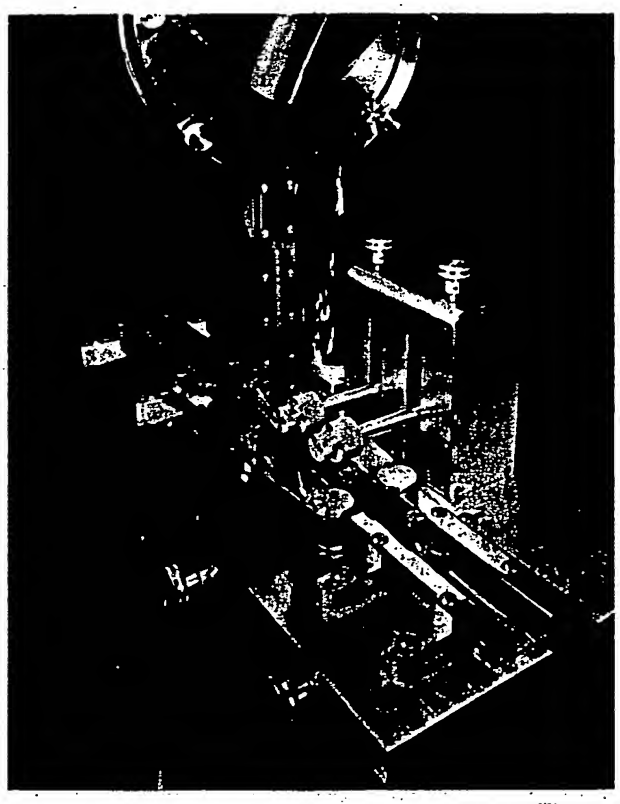

Fig. 84-27. Mechanical device for inserting rubber closures in vials (courtesy, Perry).

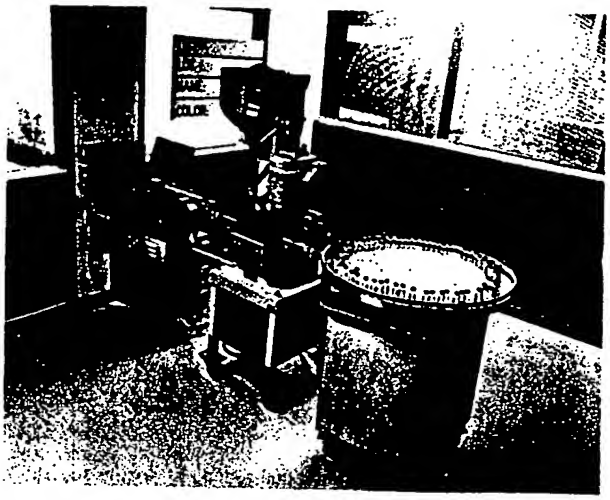

Fig. 84-28. Applying aluminum caps to vials at end of process line (courtesy, Abbott).

Fig. 84-29. A large autoclave being loaded with liter bottles of parenteral solutions (courtesy, Abbott).

stroying the aluminum cap. Therefore, an intact aluminum cap is proof that the closure has not been intentionally or unintentionally removed. Such confirmation is necessary to assure the integrity of the contents as to sterility and other aspects of quality. The aluminum caps are so designed that the outer layer of double-layered caps, or the center of single-layered caps, can be removed to expose the center of the rubber closure without disturbing the band which holds the closure in the container. Rubber closures for use with intravenous administration sets often have a permanent hole through the closure. In such cases, a thin rubber disk overlayed with a solid aluminum disk is placed between an inner and outer aluminum cap. A seal of the hole through the closure is thereby provided. These are called triple-layered aluminum caps.

Single-layered aluminum caps may be applied by means of a hand crimper known as the Fermpress.* Double- or triple-layered caps require greater force for crimping; therefore, heavy-duty mechanical crimpers are required,† as shown in Fig. 84-28.

Sterilization

Whenever possible, the parenteral product should be sterilized after being sealed in its final container and within as short a time as possible after the filling and sealing have been completed. Since this usually involves a thermal process, due consideration must be given to the effect of the elevated temperature upon the stability of the product. Many products, both pharmaceutical and biological, will be adversely affected by the elevated temperatures required for thermal sterilization. Such products must, therefore, be sterilized by a nonthermal method. Most thermolabile solutions may be sterilized by filtration through bacteria-retaining filters. Subsequently, all operations must be carried out in an aseptic manner so that contamination will not be introduced into the filtrate. To perform such an aseptic procedure is difficult, and the degree of its accomplishment is always uncertain. Colloids, oleaginous solutions, suspensions, and emulsions that are thermolabile may require a process in which each component is sterilized and the product is formulated and processed under aseptic conditions. Because of the ever-present risk of a momentary or prolonged lapse in aseptic control during an aseptic process, and the dangerous condition that could result, sterilization of a product in its final container (terminal sterilization) is preferred.

Some of the newer nonthermal methods of sterilization are finding important application to components of injections and to administration devices. Certain dry solids such as penicillin, streptomycin, polyvitamins, and certain hormones are being effectively sterilized by ionized radiations without adverse effects. Catgut sutures are now being routinely sterilized in the final package by this method. Administration sets, disposable needles and syringes, and other plastic and stainless steel equipment and components are being sterilized by ionizing radiations and by gaseous ethylene oxide sterilization. Generally speaking, however, neither of these methods may be used for liquid preparations without adverse effects on the product, and gaseous sterilization cannot be used where a glass container or other impervious barrier prevents the gas from permeating the material.

Dry-heat sterilization may be employed for a few dry solids that are not adversely affected by the high temperatures and for the relatively long heating period required. This method is most effectively applied to the sterilization of glassware and metalware. After sterilization, the equipment will be sterile, dry and, if the sterilization period is approximately doubled, pyrogen-free.

Saturated steam under pressure (autoclaving) is the most commonly used and probably the most effective method for the sterilization of aqueous liquids or substances that can be reached or penetrated by steam.

Fig. 84-29 shows liter containers of solution being loaded into an autoclave for sterilization. It is ineffective in anhydrous conditions, such as within a sealed ampul containing a dry solid or an anhydrous oil. Since the temperature employed in an autoclave is lower than that for dry-heat sterilization, equipment made of materials such as rubber and polypropylene may be sterilized. As mentioned previously, some injections will be adversely affected by the elevated temperature required for autoclaving. Sometimes the use of an autoclave designed to permit a rapid rise to sterilizing temperature and rapid cooling after the sterilizing hold-period will make it possible to use this method. For example, Dextrose Injection can be autoclaved without adverse effect if the total heating period is reduced by the use of a rapid heating and cooling cycle. Other products that will withstand autoclaving temperatures may withstand many

* Suppliers: *West, Wheaton.*
† Suppliers: *Alcoa, United Machinery, West, Wheaton.*

thermal methods such as tyndallization or inspissation. These methods may be rendered more effective for some injections by the inclusion of a bacteriostatic agent in the product.

It should be obvious that all materials subjected to sterilization must be protected from subsequent contamination to maintain their sterile state. Therefore, materials subjected to autoclaving must be wrapped or covered so that microorganisms may not gain access when removed from the autoclave. Equipment and supplies are most frequently wrapped with paper and tied or sealed with special autoclave tape. The wrapping must permit penetration of steam during autoclaving but screen out microorganisms when dry. A double wrapping with lint-free parchment paper designed for such use is probably best. Synthetic fiber cloth such as nylon or Dacron also may be used for the inner wrapping. The openings of equipment subjected to dry-heat sterilization are often covered with silver–aluminum foil or with metal or glass covers. Cellulose wrapping materials are adversely affected by the high temperatures of dry-heat sterilization.

The effectiveness of any sterilization technique must be proved before it is employed; controls then must be established to show that subsequent processes repeat the conditions proven to be effective. Since the goal of sterilization is to kill microorganisms, the ideal indicator to prove the effectiveness of the process is a biological one, resistant spores. However, many feel considerable hesitation about using biological indicators during the processing of products because of the inherent risk of inadvertent contamination of the product or the environment. Also, it has been found that the resistance of spores varies from lot to lot, thereby possibly giving false indications of reliability when used as a biological indicator for a sterilization procedure. However, others feel as strongly that biological indicators should be used, not only to prove the effectiveness of a sterilization procedure but as confirmatory evidence for the effectiveness of each sterilization process.

It is also essential to utilize other indicators to confirm the reliability of the sterilization process, such as recording thermocouples, color-change indicators, and melting indicators. Such confirmatory evidence is an essential part of the sterilization record for a product.

Further details concerning methods of sterilization and their application will be found in Chapter 78. In addition, the USP provides suggestions concerning the sterilization of injections and related materials.

Freeze-Drying

Freeze-drying (lyophilization) is a process of drying in which water is sublimed from the product after it is frozen.[14]

The particular advantages of this process are that biologicals and pharmaceuticals which are relatively unstable in aqueous solution can be processed and filled into dosage containers in the liquid state, taking advantage of the relative ease of processing a liquid; dried without elevated temperatures, thereby eliminating adverse thermal effects; and then stored in the dry state in which there are relatively few stability problems.

Further advantages include the fact that freeze-dried products are often more soluble and/or more rapidly soluble, dispersions are stabilized throughout the shelf life of the product, and products subject to degradation by oxidation have enhanced stability because the process is carried out in a vacuum.

However, the increased time and handling required for processing and the cost of the equipment limit the use of this process to those products which have significantly enhanced stability if stored in the dry state.

The fact that ice will sublime at pressures below 3 mm Hg has been a long-established laboratory principle. The extensive program for the freeze-drying of human plasma during World War II provided the impetus for the rapid development of the process.

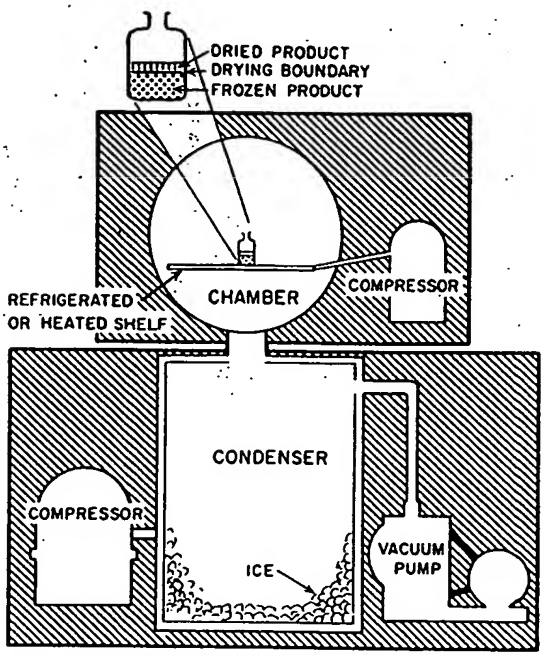

Fig. 84-30. Essential components of a freeze-drying system.

Freeze-drying essentially consists of the following:

1. Freezing an aqueous product at a temperature below its eutectic temperature.
2. Evacuating the chamber, usually below 0.1 torr (100 μm Hg).
3. Subliming ice on a cold condensing surface at a temperature below that of the product, the condensing surface being within the chamber or in a connecting chamber.
4. Introducing heat to the product under controlled conditions, thereby providing energy for sublimation at a rate designed to keep the product temperature below its eutectic temperature.

Fig. 84-30 shows such a system. The product may be frozen on the shelf in the chamber by circulating refrigerant (usually Freon, ammonia, or ethylene glycol) from the compressor through pipes within the shelf. After freezing is complete, which may require several hours, the chamber and condenser are evacuated by the vacuum pump, the condenser surface having been previously chilled by circulating refrigerant from the large compressor.

Heat is then introduced from the shelf to the product by electric resistance coils or by circulating hot water or hot glycol. The process continues until the product is dry (usually 1% or less moisture), leaving a sponge-like matrix of the solids originally present in the product, the input of heat being controlled so as not to degrade the product.

For most pharmaceuticals and biologicals the liquid product is sterilized by filtration and then filled into the dosage container aseptically. The containers must remain open during the drying process; therefore, they must be protected from contamination during transfer from the filling area to the freeze-drying chamber, while in the freeze-drying chamber, and at the end of the drying process until sealed.

Chambers may be equipped with hydraulic or rubber diaphragm internal-stoppering devices designed to push slotted rubber closures into the vials to be sealed while the chamber is still evacuated, the closures having been partially inserted immediately after filling so that the slots were open to the outside.

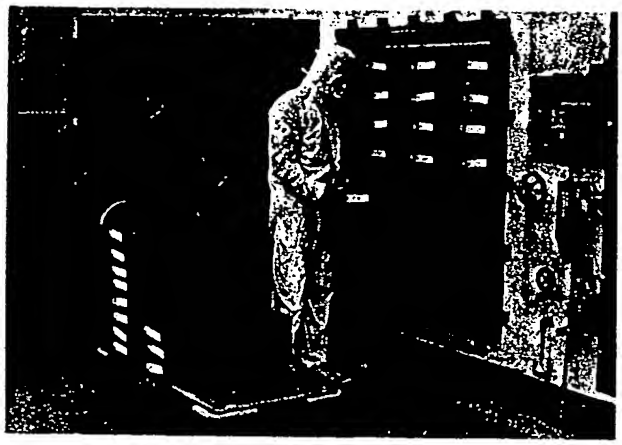

Fig. 84-31. Aseptic loading of freeze-drier (courtesy, Upjohn).

If internal stoppering is not available or containers such as ampuls are used, filtered dry air or nitrogen must be introduced to the chamber at the end of the process to establish atmospheric pressure. Then the containers must be removed and sealed under aseptic conditions. If the product is very sensitive to moisture, the environmental humidity also must be controlled until it is sealed.

Factors Affecting the Process Rate—The greater the depth of the product in the container, the longer will be the drying process. Therefore, a product to be frozen by placing the container on a refrigerated shelf (plug freezing) should be filled to a planned, limited depth. If a large volume of solution must be processed, the surface area may be increased and the depth decreased by freezing the solution on a slant or while rotating the container on an angle (shell freezing) in a liquid refrigerant bath, such as dry ice and alcohol.

The actual driving force for the process is the vapor pressure differential between the vapor at the surface where drying of the product is occurring (the drying boundary) and the vapor pressure at the surface of the ice on the condenser. The latter is determined by the temperature of the condenser as modified by the insulating effect of the accumulated ice. The former is determined by a number of factors, including:

1. The rate of heat conduction through the container and the frozen material, both usually relatively poor thermal conductors, to the drying boundary while maintaining all of the product below its eutectic temperature.
2. The impeding effect of the increasing depth of dried porous product above the drying boundary.
3. The temperature and heat capacity of the shelf itself.

This may be visualized by referring to Fig. 84-30.

The passageways between the product surface and the condenser surface must be wide open and direct for effective operation. Therefore, the condensing surfaces in large freeze-driers are usually in the same chamber as the product. Evacuation of the system is necessary to reduce the impeding effect that collisions with air molecules would have on the passage of water molecules. However, the residual pressure in the system must be greater than the vapor pressure of the ice on the condenser or the ice will be vaporized and pulled into the pump, an event detrimental to most pumps.

The amount of solids in the product, their particle size, and their thermal conductance will affect the rate of drying. The more solids present, the more impediment will be provided to the escape of the water vapor. The smaller the particle size, particularly the crystal size of the ice, the faster the drying generally will be. The poorer the thermal conducting properties of the solids in the product, the slower will be the rate of transfer of heat through the frozen material to the drying boundary.

The rate of drying is essentially slow, most often requiring 24 hours or longer for completion. The actual time required, the rate of heat input, and the product temperatures that may be utilized must be determined for each product and then carefully reproduced with successive processes.

Factors Affecting Formulation—The active constituent of many pharmaceutical products is present in such a small quantity that if freeze-dried alone its presence would be hard to detect visually. Therefore, substances are often added to increase the amount of solids present.

Some consider it ideal for the dried product plug to occupy essentially the same volume as that of the original solution. To achieve this, the solids content of the original product must be between approximately 10 and 25%. Among the substances found most useful for this purpose, usually as a combination, are sodium or potassium phosphates, citric acid, tartaric acid, gelatin, and carbohydrates such as dextrose, mannitol, and dextran.

Each of these substances contributes appearance characteristics to the plug, such as whether dull and spongy or sparkling and crystalline, firm or friable, expanded or shrunken, and uniform or striated. Therefore, the formulation of a product to be freeze-dried must include consideration not only of the nature and stability characteristics required during the liquid state, both freshly prepared and when reconstituted before use, but the characteristics desired in the dried plug.

Modifications in the Process and Equipment—In some instances a product may be frozen in a bulk container or in trays rather than in the final container and then handled as a dry solid. This may be desirable when large volumes of a product are processed.

Heat may be introduced to all sides of the product by radiation from infrared sources, rather than only from the bottom as with conductive heating. While this generally increases the rate of drying, there are at least two major disadvantages to radiant heating of pharmaceuticals; these are (1) multiple containers produce shadowing with resultant blockage of the radiations and (2) the dried material on the outside of the frozen product may be scorched easily by the heat as drying progresses.

When large quantities of material are processed it may be desirable to utilize ejection pumps in the equipment system. These draw the vapor into the pump and eject it to the outside, thereby eliminating the need for a condensing surface. Such pumps are expensive and usually practical only in large installations.

Available freeze-driers* range in size from small laboratory units to large industrial models such as those shown in Fig. 84-31. Their selection requires consideration of such factors as tray area required, volume of water to be removed, whether or not aseptic processing will be involved, is internal stoppering required, will separate freezers be used for initial freezing of the product, and the degree of automatic operation desired.

Freeze-drying is now being utilized for research in the preservation of human tissue and is finding increasing application in the food industry. Progress on new developments is being made in both the process and the equipment.

* Suppliers: *Hull, Industrial Dynamics, NRC, Repp, Stokes, Vacuum, Virtis.*

Quality Control

The importance of undertaking every possible means to be assured of the quality of the finished product cannot be overemphasized. Every component and every step of the manufacturing process must be subjected to intense scrutiny to be confident that quality is attained in the finished product. The responsibility for supervising this is a grave one, and lapses of requirements or short cuts in procedure may not be permitted. Such responsibility applies wherever parenteral preparations are manufactured.

The principles of quality control are basically the same for the manufacture of any pharmaceutical. These are discussed in Chapter 82. During the discussion of the preparation of injections, mention was made of numerous quality requirements for components and manufacturing processes. Here, only certain tests characteristically applicable to parenteral preparations will be discussed.

Sterility Test

All lots of injections in their final containers must be tested for sterility. The USP prescribes the requirements for this test for official injections. The Food and Drug Administration uses these requirements as a guide for testing unofficial sterile products. The official test has acknowledged limitations in the information that it can provide. Therefore, it should be noted that this test is not intended as a thoroughly evaluative test for a product subjected to a sterilization method of unknown effectiveness. It is intended primarily as a check test on the repetition of a previously proved sterilization procedure, or to give assurance of its continued effectiveness. A discussion of sterility testing is given in Chapter 78.

It should be noted that a "lot" with respect to sterility testing is that group of product containers which has been subjected to the same sterilization procedure. For containers of a product which have been sterilized by autoclaving, for example, a lot would constitute those processed in a particular sterilizer cycle. For an aseptic filling operation, a lot would constitute all of those product containers filled during a period when there was no change in the filling assembly or equipment and which is no longer than one working day or shift.

Pyrogen Test

The presence of pyrogens in parenteral preparations is evaluated by a qualitative fever response test in rabbits. The USP test is described in Chapter 31. Rabbits are used as test animals because they show physiologic response to pyrogenic substances similar to that by man. While a minimum pyrogenic dose (MPD), the amount just sufficient to cause a positive USP Pyrogen Test response, may sometimes produce uncertain test results, a content equal to a few times the MPD will leave no uncertainty. Therefore, the test is valid and has remained first in choice since introduced by Seibert in 1923. It should be understood that not all injections may be subjected to the pyrogen test since the medicinal agent may have a physiologic effect on the test animal such that any fever response would be masked. Therefore, the pyrogen test is performed primarily on vehicles.

A new test for pyrogens is receiving much favorable consideration. It is an *in vitro* test based on the gelling of a pyrogenic preparation in the presence of the lysate of the amebocytes of the horseshoe crab (*Limulus polyphemus*). The Limulus Test, as it is called, appears to be simpler, more rapid, and of greater sensitivity than the rabbit test.[15] Although it detects only the endotoxic pyrogens of gram-negative bacteria, this probably will not significantly limit its use since most environmental contaminants gaining entrance to sterile products are gram-negative.

Clarity Tests

The USP does not provide specifications for a clarity test. It contains only the statement that good manufacturing practice requires that each final container of an injection should be subjected individually to a visual inspection. The development of test procedures to meet this general requirement is the responsibility of the manufacturer.

The objective of the clarity inspection is to prevent the distribution and use of parenterals which contain particulate matter that may be psychologically or actually harmful to the recipient. Solutions to be introduced intravenously require the most critical evaluation.

Until recently, concern about particulate matter in parenteral solutions was limited largely to the psychological effect on the user in that the presence of visible "dirt" would suggest that the product was of inferior quality; however, further investigation has caused a new assessment to be undertaken of the significance of particles in solutions to be introduced into the blood stream. While data defining the extent and risk of toxic effects is still rather nebulous, it has been shown that particles of lint, rubber, insoluble chemicals, and other foreign particulate matter can produce emboli in vital organs of animals and man. A recent study suggests that another adverse physiologic effect may be related to the presence of particulate matter in intravenous fluids, namely, the development of infusion phlebitis.

A study of the size distribution of particulate matter in commercial intravenous solutions showed that the number of particles increased approximately logarithmically with decreasing size. This finding would suggest that a count made at an arbitrarily chosen size could be used to predict the number of particles at another size. The counts were made with a Coulter Counter, a resistance-type counter. Other electronic counters utilize the light-scattering* or light-shadowing† principle to count particles in a liquid sample. Particles may also be counted and examined microscopically by collection on the surface of a membrane filter, a method that permits identification of the particles as well as a count. Methods of particulate evaluation such as these are performed on a sample from a container. Such methods cannot be utilized for the in-line evaluation of every container produced commercially, but may be used for quality-control sampling of the process.

The particle size that should be of particular concern has not been determined but it has been suggested that, since erythrocytes have a diameter of approximately 4.5 μm, particles of more than 5 μm should be the basis for evaluation. This is a considerably smaller particle than can be seen with the unaided eye; approximately 50 μm is the lower limit unless the Tyndall effect is utilized, whereby particles as small as 10 μm may be seen by the light scattered from them.

Meanwhile, the product units from the production line are being inspected individually by human inspectors under a good light, baffled against reflection into the eye, against a black and a white background. Although this inspection is subject to the limitations in the size of particles that can be seen, the variation in visual acuity from inspector to inspector, the emotional state of the inspector, eye strain and fatigue, and other personal factors that will affect what the inspector sees, it does provide a means for eliminating the normally few units which contain visible particles and it is a check on the repetition of the standard clean processing procedure established for that product.

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* Suppliers: *Climet, Royco.*
† Supplier: *HIAC.*

This concern over the presence of particulate matter in parenteral products, particularly those given intravenously, has brought about a dramatic improvement through the voluntary effort of the pharmaceutical industry. One study[16] clearly shows a reduced particulate content of commercially prepared intravenous infusion fluids, as compared with earlier work. Also, it has been shown that additives and administration sets may introduce a substantial amount of particulate matter to an otherwise relatively clean solution. In addition, the technique utilized in the hospital for the preparation and administration of the intravenous infusion fluid must be carefully controlled to avoid the introduction of particulate matter. Therefore, the pharmaceutical manufacturer, the administration set manufacturer, the hospital pharmacist, the nurse, and the physician must share responsibility for making sure that the patient receives a clean intravenous injection.

Leaker Test

Ampuls that have been sealed by fusion must be subjected to a test to determine whether or not a passageway remains to the outside. If such a passageway remains, all or a part of the contents of the ampul may leak to the outside and spoil the package, or microorganisms or other contaminants may enter. Changes in temperature during storage cause expansion and contraction of the ampul and contents, and will accentuate interchange if a passageway exists.

A leaker test is usually performed by producing a negative pressure within an incompletely sealed ampul while the ampul is entirely submerged in a deeply colored dye solution. Most often, approximately a 1% methylene blue solution is employed. The test may be performed by subjecting the ampuls to a vacuum in a vacuum chamber, the ampuls being submerged in a dye bath throughout the process. Another procedure frequently employed is to simply autoclave the ampuls in a dye bath. A modification of this is to remove them from the autoclave while hot and quickly submerge them in a cool bath of dye solution. After carefully rinsing the dye solution from the outside, color from the dye will be visible within a leaker. Leakers are, of course, discarded.

Vials and bottles are not subjected to a leaker test because the sealing material (rubber stoppers) is not rigid. Therefore, results from such a test would be meaningless. However, evacuated bottles containing a liquid may be checked for a sharp "click" sound produced when struck with an implement such as a rubber mallet.

Safety Test

The National Institutes of Health requires of most biological products routine safety testing in animals. Under the Kefauver-Harris Amendments to the Federal Food, Drug, and Cosmetic Act, most pharmaceutical preparations are now required to be tested for safety. Because it is entirely possible for a parenteral product to pass the routine sterility test, pyrogen test, and chemical analyses and still cause unfavorable reactions when injected, a safety test in animals is essential to provide additional assurance that the product does not have unexpected toxic properties. Safety tests in animals are discussed in detail in the USP.

Packaging and Labeling

A full discussion of the packaging of parenteral preparations is beyond the scope of this text. It is essential, of course, that the packaging should provide ample protection for the product against physical damage from shipping, handling, and storage and should protect light-sensitive materials from ultraviolet radiation.

Packaging—The USP includes certain requirements for the packaging and storage of injections, as follows:

1. The volume of injection in single-dose containers is defined as that which is specified for parenteral administration at one time and is limited to a volume of 1 liter.
2. Parenterals intended for intraspinal, intracisternal, or peridural administration are packaged only in single-dose containers.
3. Unless an individual monograph specifies otherwise, no multiple-dose container shall contain a volume of injection more than sufficient to permit the withdrawal and administration of 30 ml.
4. Injections packaged for use as irrigation solutions or for hemofiltration or dialysis are exempt from foregoing requirements relating to packaging. Containers for injections packaged for use as hemofiltration or irrigation solutions may be designed to empty rapidly and may contain a volume in excess of 1 liter.
5. Injections intended for veterinary use are exempt from the packaging and storage requirements concerning the limitation to single-dose containers and to volume of multiple-dose containers.

Labeling—The labeling of an injection must provide the physician or other user with all of the information needed to assure the safe and proper use of the therapeutic agent. Since all of this information cannot be placed on the immediate container and be legible, it may be provided on accompanying printed matter. General labeling requirements for drugs are discussed in Chapter 106.

A restatement of the labeling definitions and requirements of the USP for Injections is as follows:

The term "labeling" designates all labels and other written, printed, or graphic matter upon an immediate container or upon, or in, any package or wrapper in which it is enclosed, with the exception of the outer shipping container. The term "label" designates that part of the labeling upon the immediate container.

The label states the name of the preparation, the percentage content of drug of a liquid preparation, the amount of active ingredient of a dry preparation, the volume of liquid to be added to prepare an injection or suspension from a dry preparation, the route of administration, a statement of storage conditions, and an expiration date. Also, the label must indicate the name of the manufacturer or distributor and carry an identifying lot number. The lot number is capable of providing access to the complete manufacturing history of the specific package, including each single manufacturing step.

The container label is so arranged that a sufficient area of the container remains uncovered for its full length or circumference to permit inspection of the contents.

The label must state the name of the vehicle and the proportions of each constituent, if it is a mixture; the names and proportions of all substances added to increase stability or usefulness; and the expiration date where required by the individual monograph.

Preparations labeled for use as irrigating solutions must meet the requirements for Injections other than those relating to volume and also must bear on the label statements that they are not intended for intravenous injection.

Injections intended for veterinary use are so labeled.

References

1. Griffenhagen GB. *Bull Parenteral Drug Assoc 16(2):* 12, 1962.
2. Tousignaut DR. *Am J Hosp Pharm 34:* 943, 1977.
3. Bergman DH. *Drug Intel Clin Pharm 11:* 345, 1977.
4. Spiegel AJ, Noseworthy MM. *J Pharm Sci 52:* 917, 1963.
5. Schroeter LC. *J Pharm Sci 50:* 891, 1961.
6. Autian J. *Bull Parenteral Drug Assoc 22:* 276, 1968.
7. Subrahmanyam SV, Majeske JP. *Am J Pharm 129:* 222, 1957.
8. Hopkins GH. *J Pharm Sci 54:* 138, 1965.
9. Federal Std. No. 209b, GSA, Washington, DC 20407, April 2, 1973.
10. Anschel J. *Bull Parenteral Drug Assoc 31:* 47, 1977.
11. Grimes TL, Fonner DE, *et al. Bull Parenteral Drug Assoc 31:* 1977.
12. Macek TJ. *J Pharm Sci 52:* 694, 1963.
13. Nash RA. *Drug Cosmet Ind 97:* 843, 1965; *98:* 39, 1966.
14. *Ann NY Acad Sci, 85:* 501–734, 1965.
15. Cooper JF. *Bull Parenteral Drug Assoc 29:* 122, 1975.
16. Turco SJ, Davis NM. *Am J Hosp Pharm 30:* 557, 1973.

Bibliography

Martin EW, *et al.: Techniques of Medication,* Lippincott, Philadelphia, 1969.

Avis KE, Miller WA, in Hoover JE, ed: *Dispensing of Medication,* ed, Mack Publ. Co., Easton, PA, Chap. 10, 1976.

Avis KE, in Lachman L, *et al.: The Theory and Practice of Ind*

Pharmacy, 2nd ed, Lea & Febiger, Philadelphia, Chaps. 20 and 21, 1976.

Turco S, King RE: *Sterile Dosage Forms*, Lea & Febiger, Philadelphia, 1979.

Avis KE, *et al.*: *Parenteral Dosage Forms—An Annotated Bibliography*, 5 vols, (1959–63, 1964–67, 1968–70, 1971–72, 1973). Parenteral Drug Assoc., Philadelphia.

Useller JW: *Clean Room Technology* (NASA SP-5074), USGPO, Washington, DC, 1969.

Perkins JJ: *Principles and Methods of Sterilization in Health Sciences*, 2nd ed, Thomas, Springfield, IL, 1969.

Block SS: *Disinfection, Sterilization and Preservation*, 2nd ed, Lea and Febiger, Philadelphia, 1977.

Phillips GB, Miller WS, eds: *Industrial Sterilization*, Duke Univ. Press, Durham, NC, 1973.

Gaughran ERL, Kereluk K, eds: *Sterilization of Medical Products*, Johnson & Johnson, New Brunswick, NJ, 1977.

Meryman HT, ed: *Cryobiology*, Academic, New York, 1966.

Chapter 85

Intravenous Admixtures

intravenous fluids
packaging systems
administration sets
administration procedures
admixtures
total parenteral nutrition
parenteral prescriptions

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It has been estimated that 40% of all drugs administered in hospitals are given in the form of injections and their use is increasing. Part of this increase in parenteral therapy is due to the wider utilization of intravenous fluids (IV fluids). In the last decade the use of IV fluids has doubled, increasing from 150 million units to 250 million units annually. Not only do IV fluids continue to serve as the means for fluid replacement, electrolyte-balance restoration, and supplementary nutrition, but they are also playing major roles as vehicles for other drug substances and in total parenteral nutrition. Intravenous fluids are finding greater use as the means of administering other drugs because of convenience, the means of reducing the irritation potential of the drugs, and the desirability for continuous and intermittent drug therapy. The techniques for providing total parenteral nutrition parenterally have improved steadily in the last decade and such use is increasing at the rate of 40% annually. The use of IV fluids for these purposes requires the compounding of specific intravenous admixtures (parenteral prescriptions) to meet the clinical needs of a given patient. However, the combination of drug substances in an intravenous fluid can promote parenteral incompatibilities and give rise to conditions not favorable for drug stability. A new area of specialization has been created for hospital pharmacists who can develop the expertise to prepare these solutions, recognizing their compatibility and stability problems and the potential for contamination, and to participate in the administration of the solutions. The complex compounding of an order for total parenteral nutrition requires knowledgeable personnel capable of making accurate calculations, compounding, and having perfect aseptic technique. The parenteral prescription is becoming increasingly important in hospitals. Centralized admixture programs are now found in 50% of the nation's hospitals having 300 beds or more. Equipment available for administering intravenous fluids has become more sophisticated, and has made possible increased accuracy of dosage and led to the development of new concepts and methods of nutrition and drug treatment.

Intravenous Fluids

Large-volume injections intended to be administered by intravenous infusion are commonly called IV fluids and are included in the group of sterile products referred to as large-volume parenterals. Large-volume parenterals consist of single-dose injections having a volume of 100 ml or more and containing no added substances. Intravenous fluids are packaged in containers having a capacity of 150 ml to 1000 ml. Minitype infusion containers of 250-ml capacity are available with 50- and 100-ml partial fills for solution of drugs when used in the "piggyback" technique. This technique refers to the administration of a second solution through a Y-tube or gum-rubber connection in the administration set of the first intravenous fluid, thus avoiding the need for another injection site. In addition to the IV fluids, the group also includes irrigation solutions and solutions for dialysis.

Intravenous fluids are sterile solutions of simple chemicals such as sugars, amino acids, or electrolytes—materials which can easily be carried by the circulatory system and assimilated. Prepared with Water for Injection USP, the solutions are pyrogen-free. Because of the large volumes administered intravenously, the absence of particulate matter assumes a more significant role in view of possible biological hazards resulting from particulate matter. Absence of particulate matter or clarity of IV fluids is as important at the time of administration following their manipulation in the hospital as it is at the time of injection manufacture.

Limits for particulate matter occurring in IV fluids, or large-volume injections used for single-dose infusion, have been defined in the USP. This represents the first regulatory attempt to define limits for particulate matter in parenterals. These limits do not apply to multiple-dose injections, small-volume injections, or injections prepared by reconstitution from sterile solids. The USP defines particulate matter as extraneous, mobile, undissolved substances, other than gas bubbles, unintentionally present in parenteral solutions. The microscopic membrane method is used for determining the presence and size distribution of the particles observed. The determination is carried out in a laminar airflow hood using ultraclean equipment. The IV fluid sample is placed in an ultraclean funnel containing an ultraclean grid membrane through which the sample passes. After the particulate matter is collected on the membrane, the membrane is rinsed and dried within the hood. The entire surface of the membrane is examined within the hood, using a suitable microscope under 100× magnification. The total numbers of particles having effective linear dimensions equal to or larger than 10.0 μm and larger than 25.0 μm are counted. The fluid meets the requirement of the test if it contains not more than 50 particles per ml that are equal to or larger than 10 μm, and not more than 5 particles per ml that are equal to or larger than 25.0 μm in linear dimensions.

Intravenous fluids are commonly used for a number of clinical conditions. These include: (1) correction of disturbances in electrolyte balance; (2) correction of disturbances in body fluids (fluid replacement); (3) the means of providing basic nutrition; (4) the basis for the practice of providing total parenteral nutrition (TPN) or parenteral hyperalimentation; and (5) use as vehicles for other drug substances. In both the latter two cases it has become common practice to add other drugs to certain IV fluids to meet the clinical needs

Table I—IV Fluids Commonly Used For Intravenous Admixtures

Injection	Concentration	pH	Therapeutic Use
Amino Acid (Synthetic)			Fluid and nutrient replenisher
Aminosyn (Abbott)	3.5%; 7%	5.25	
FreAmine II (McGaw)	8.5%	6.6	
Travasol (Travenol)	5.5%; 8.5%	6.0	
Veinamine (Cutter)	8%	6.2–6.6	
Dextrose (Glucose, D5/W)	2.5%–50%	3.5–6.5	Fluid and nutrient replenisher
Dextrose and Sodium Chloride	Varying concn of dextrose from 5%–20% with varying concn of sodium chloride from 0.11%–0.9%	3.5–6.5	Fluid, nutrient, and electrolyte replenisher
Fructose (Levulose)	10%	3.0–6.0	Fluid and nutrient replenisher
Fructose and Sodium Chloride	10% 0.9%	3.0–6.0	Fluid, nutrient, and electrolyte replenisher
Invert Sugar	5%, 10%	4.0	Fluid and nutrient replenisher
Lactated Ringer's (Hartmann's)		6.0–7.5	Systemic alkalizer; fluid and electrolyte replenisher
NaCl	0.6%		
KCl	0.03%		
$CaCl_2$	0.02%		
Na Lactate	0.3%		
Protein Hydrolysate Amigen (Travenol) Aminosol (Abbott) CPH-5 (Cutter) Hyprotigen (McGaw)	5% from either casein or fibrin	5.0–7.0	Fluid and nutrient replenisher
Ringer's		5.0–7.5	Fluid and electrolyte replenisher
NaCl	0.86%		
KCl	0.03%		
$CaCl_2$	0.033%		
Sodium Chloride	0.45%; 0.9%; 3%; 5%	4.5–7.0	Fluid and electrolyte replenisher
Sodium Lactate	1/6 M	6.3–7.3	Fluid and electrolyte replenisher

the patient. Using IV fluids as vehicles offers the advantages of convenience, the means of reducing the irritation potential of the drug, and provides a method for continuous drug therapy. However, the practice requires that careful consideration be given to the stability and compatibility of additives present in the IV fluids serving as vehicles. This approach also demands strict adherence to aseptic techniques in adding the drugs, as well as in the administration of the IV fluids. These procedures are discussed later in the chapter. The IV fluids commonly used for parenteral admixtures are shown in Table I.

Many disease states result in electrolyte depletion and loss. Proper electrolyte concentration and balance in plasma and tissues are critical for proper body function. Electrolyte restoration and balance are most rapidly achieved through administration of IV fluids. Required electrolytes include sodium and chloride ions, which in normal saline more closely approximate the composition of the extracellular fluid than solutions of any other single salt; potassium, the principal intracellular cation of most body tissues and an essential for the functioning of the nervous and muscular systems as well as the heart; magnesium, as a nutritional supplement especially in hyperalimentation solutions; and phosphate ion, important in a variety of biochemical reactions. In addition to the number of standard electrolyte fluids shown in Table I, a large number of combinations of electrolytes in varying concentrations are available commercially. Some of these electrolyte fluids also contain dextrose and vitamins.

Dextrose Injection 5% is the most frequently used IV fluid, either for nutrition or fluid replacement. It is isotonic and administered intravenously into a peripheral vein. One gram of dextrose provides 3.4 Calories and a liter of Dextrose Injection 5% supplies 170 Calories. The body utilizes dextrose at a rate of 0.5 g per kilogram of body weight per hour. More rapid administration can result in glycosuria. Therefore a liter of Dextrose Injection 5% requires one and one-half hours for assimilation. The pH range of Dextrose Injection 5% can vary from 3.5 to 6.5. The wide range permitted is due to the free sugar acids present and formed during the sterilization and storage of the injection. To avoid incompatibilities when other drug substances are added to Dextrose Injection, the possible low pH should be considered in using it as a vehicle. More concentrated solutions of dextrose are available and provide increased calorie intake with less fluid volume. Being hypertonic, the more concentrated solutions may be irritating to peripheral veins. Highly concentrated solutions are administered only in a larger central vein. Other IV fluids used for intravenous admixtures and providing calories include solutions of fructose (levulose) and those containing invert sugar. There is some evidence that fructose, unlike dextrose, may be used in diabetic patients; the 10% injection is hypertonic and provides 375 calories per liter. Invert sugar consists of equal parts of dextrose and levulose; it is claimed that the presence of levulose promotes more rapid utilization of dextrose.

Intravenous fluids containing crystalline amino acids or low-molecular-weight peptides hydrolyzed from casein or fibrin can provide biologically utilizable amino acids for protein

synthesis (Chapter 52, p. 970). Protein contributes to tissue growth, wound repair, and resistance to infection. The protein requirement for the normal adult is 1 g per kilogram of body weight per day; children and patients under stress require greater amounts. Attempts are made to maintain a positive nitrogen balance, indicating that the protein administered is being properly utilized and not broken down and eliminated through the urine as creatinine and urea, which are normal waste products. In positive nitrogen balance the patient is taking in more nitrogen than he is eliminating. In negative nitrogen balance there is more nitrogen being eliminated through the urine regularly than is being administered intravenously. This means that tissues are continuing to be torn down and repair is not necessarily taking place. Protein Hydrolysate Injection and Amino Acid Injection can afford the total body requirements for proteins by the procedure known as total parenteral nutrition (discussed below), or be used for supplemental nutrition by peripheral administration. In addition to the amino acids or peptides, these nutritional injections may also contain dextrose, electrolytes, vitamins, and insulin. Fat emulsion (*Intralipid*, Cutter; *Liposyn*, Abbott) is sometimes used concurrently but administered at another site.

Packaging Systems

Containers for intravenous fluids must be designed to maintain solution sterility, clarity (freedom from particulate matter), and nonpyrogenicity from the time of preparation, through storage, and during clinical administration. Container closures must be designed to facilitate insertion of administration sets through which the injections are administered at a regulated flow-rate into suitable veins. IV fluids are available in glass and plastic containers; the latter may be made from either a flexible or semirigid plastic material. IV fluids are supplied in 1000-ml, 500-ml, and 250-ml sizes in addition to 250-ml capacity containers packaged with 50 or 100 ml of Dextrose Injection 5% or Sodium Chloride Injection for piggyback use. IV fluids in glass containers are packaged under vacuum, which must be dissipated prior to use. For fluid to leave the IV glass container and flow through the administration set, some mechanism is necessary to permit air to enter the container. Current flexible plastic systems do not require air introduction in order to function. Atmospheric pressure pressing on the container forces the fluid to flow.

All glass and plastic containers are single-dose and should be discarded if not used after opening. Intravenous fluids are packaged with approximately 3% excess fill to allow for removal of air from the administration set and permit the labeled volume to be delivered from the container. The containers are graduated at 20-ml increments on scales that permit the volume in container to be determined either from an upright or inverted position. Glass containers have aluminum bands for hanging while plastic containers have eyelet openings or plastic straps for attachment to IV poles.

IV fluids are available from four sources. With the exception of those from Cutter Laboratories, all provide both glass and plastic containers. The glass-container systems of Travenol/Baxter and McGaw are similar, as are the system designs of Abbott and Cutter Laboratories. The characteristics of current packaging systems are summarized in Table II.

Table II—IV Fluid Systems

Source	Container	Characteristics
Travenol/Baxter	Glass	Vacuum Air tube
Travenol/Baxter (Viaflex®)	Plastic	Polyvinyl chloride Flexible Non-vented
McGaw	Glass	Vacuum Air tube
McGaw (Accumed®)	Plastic	Polyolefin Semirigid Non-vented
Abbott	Glass	Vacuum Air filter*
Abbott (Lifecare®)	Plastic	Polyvinyl chloride Flexible Non-vented
Cutter	Glass	Vacuum Air filter*

* Part of administration set.

Administration Sets

Administration sets used to deliver fluids intravenously are sterile, pyrogen-free, and disposable. Although these sets are supplied by different manufacturers, each for its own system, they have certain basic components. These include a plastic spike to pierce the rubber closure or plastic seal on the IV container; a drip (sight) chamber to trap air and to permit adjustment of flow rate; and a length (60 to 180 in) of polyvinyl chloride tubing terminating in a gum-rubber injection port. At the tip of the port is a rigid needle or catheter adapter. An adjustable clamp (screw or roller type) on the tubing pinches the tubing to regulate flow. Since the gum-rubber port is self-sealing, additional medication can be added to the IV system at these ports of entry. Glass containers that have no

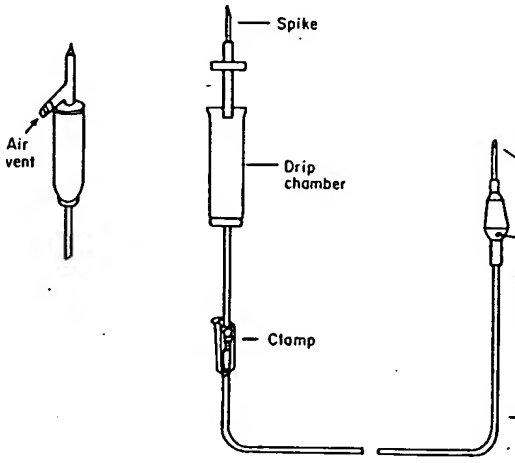

Fig. 85-1. Parts of basic administration sets.

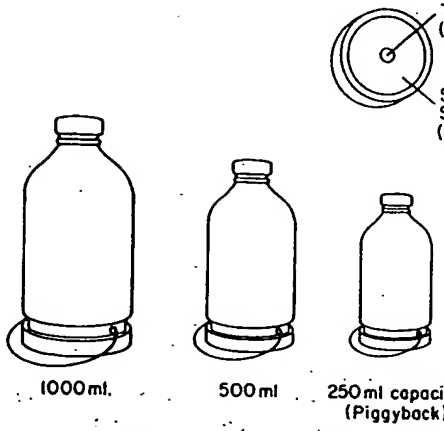

Fig. 85-2. Abbott and Cutter IV glass container. The air ve... provided through the air filter located in the spike of the adminis... set. See Fig. 85-1.

air tubes require air-inlet filters designed as part of the administration set (Abbott, Cutter). See Figs. 85-1 to 85-5.

Administration Procedures

In the administration of IV fluids, the primary IV container provides for fluid replacement, electrolyte replenishment, drug therapy, or nutrition; the fluid can be infused over a 4- to 8-hour period. In some cases an IV fluid is slowly infused for the purpose of keeping the vein open (KVO). This will allow additional drugs to be administered when required. The primary IV fluid can also serve as a vehicle for other drugs to be administered. This would then become an intravenous admixture (IV drip) and results in continuous blood levels of added drugs once the steady-state has been reached.

In preparing an IV fluid for administration, the following procedure is used.

1. The spike adapter of the administration set is inserted into stopper or seal of the IV container. Fig. 85-5.
2. The IV fluid is hung on a stand at bedside and air is purged from the administration set by opening clamp until fluid comes out of needle. The tubing is then clamped off. Fig. 85-5.
3. The venipuncture is made by member of the IV team, floor nurse or physician.
4. The infusion rate is adjusted by slowly opening and closing clamp until the desired drop rate, viewed in the drip chamber, is obtained. The usual running time is 4 to 8 hours (usually 125 ml are delivered in one hour). Drugs such as heparin, insulin, lidocaine, and dopamine may be present in the IV drip. When potent drugs are present, the flow-rates will vary and be dependent on the clinical condition of the patient. Sets are calculated to deliver 10, 15, 20, 50 or 60 drops per ml depending on manufacturer. Fig. 85-5.

Intermittent administration of an antibiotic and other drugs can be achieved by any of three methods. These are by (1) direct intravenous injection (IV bolus or push), (2) addition of the drug to a predetermined volume of fluid in a volume-control device, or (3) use of a second container (minibottle, minibag) with an already hanging IV fluid (piggybacking).

Direct Intravenous Injection—Small volumes (1 to 50 ml) of drugs are injected into the vein over a short period of time (1 to 5 minutes). The injection can also be made through a resealable gum-rubber injection site of an already hanging IV fluid. This method is suitable for a limited number of drugs but too hazardous for most drugs.

Volume-Control Method—Volume-control sets provide a means for intermittent infusion of drug solutions in precise quantities, at controlled rates of flow. These units consist of calibrated plastic fluid-chambers placed in a direct line under an established primary IV container or more often attached to an independent fluid supply. In either case, the drug to be administered is first reconstituted if it is a sterile solid and injected into the gum-rubber injection port of the volume-control unit. It is then further diluted to 50 to 150 ml with the primary fluid or the separate fluid reservoir. Administration of the total drug-containing solution requires 30 to 60 minutes and produces a peak concentration in the blood followed by a valley if the dosage is discontinued. The following volume control sets are available commercially: *Soluset®*, Abbott; *Buretrol®*, Travenol/Baxter; *Metriset®*, McGaw; and *Volutrol®*, Cutter.

The procedure for setting up an intermittent IV infusion with a volume-control set is as follows:

1. Using aseptic technique, the spike of the volume control set is inserted into the primary IV fluid or a separate fluid container. See Fig. 85-7.
2. Air is purged from tubing of the volume control set by opening clamps until fluid comes through. See Fig.
3. The clamp is opened above the calibrated chamber and it is filled with 25 to 50 ml fluid from the primary IV container or separate fluid container.
4. The clamp is closed above the chamber.
5. The medication is injected through the gum-rubber port of the volume-control unit.

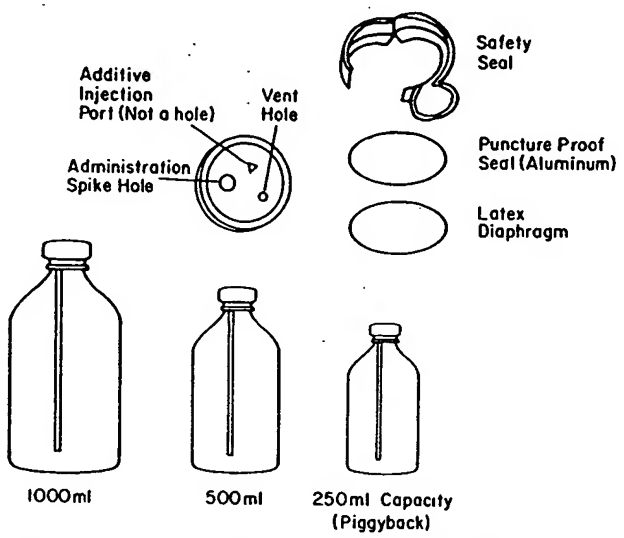

Fig. 85-3. Travenol/Baxter and McGaw glass container. The plastic air tube allows the air to enter the bottle as the fluid is infused into the patient. The spike of the administration set is not vented. See Fig. 85-1.

6. The clamp above the chamber is opened to complete the dilution to the desired volume (50 to 150 ml), then closed.
7. Flow commences when clamp below volume-control unit is opened.

Piggyback Method—The piggyback method refers to the intermittent intravenous drip of a second solution, the reconstituted drug, through the venipuncture site of an estab-

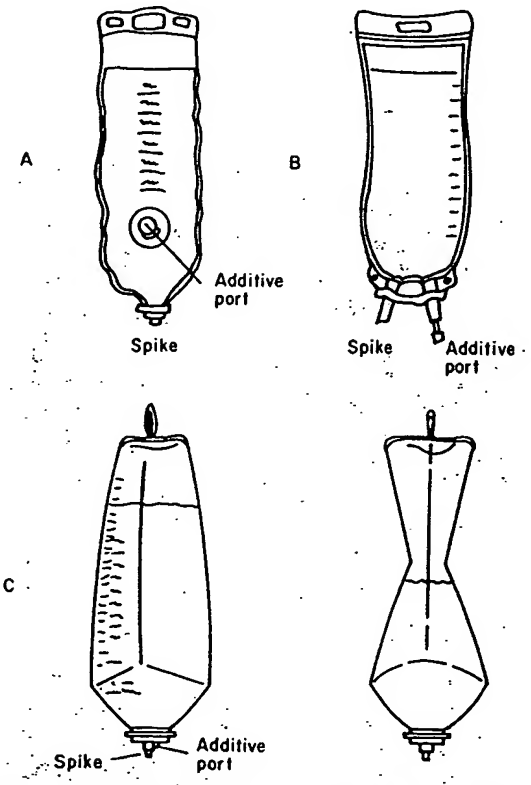

Fig. 85-4. (A) Abbott (Lifecare®) polyvinyl chloride flexible container; (B) Travenol/Baxter (Viaflex®) polyvinyl chloride flexible container; McGaw (Accumed®) polyolefin semirigid container, front and side views. These containers take non-vented administration sets. See Fig. 85-1.

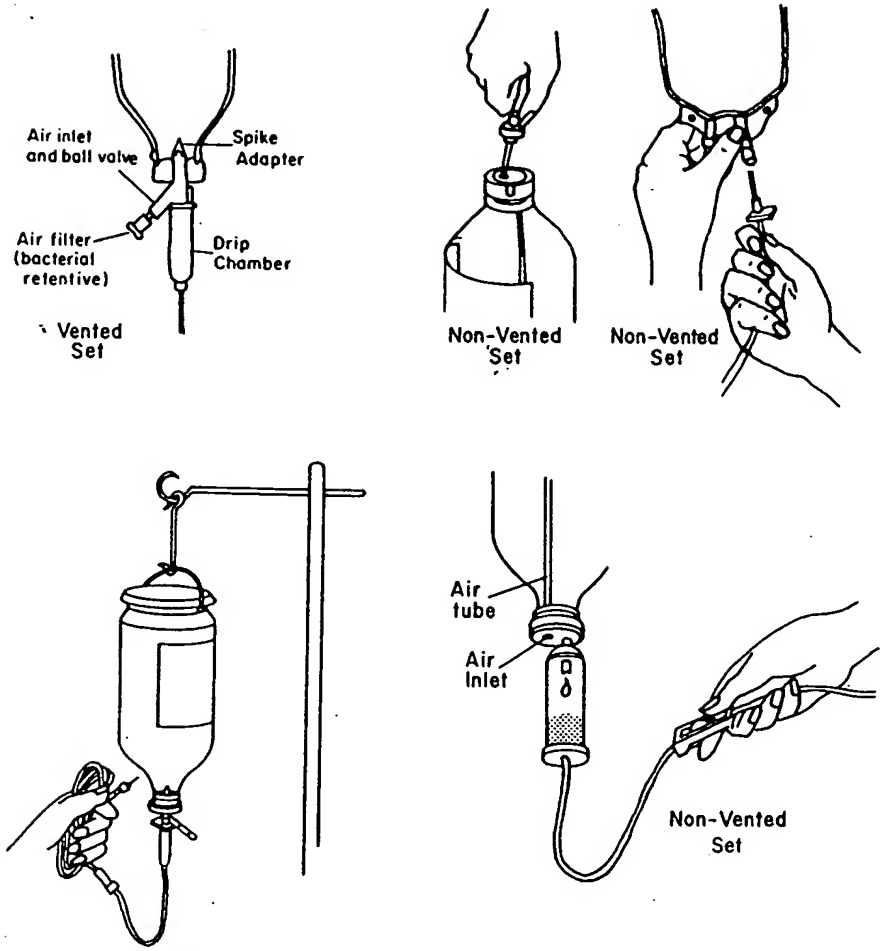

Fig. 85-5. Setting up primary IV fluid for administration.

Fig. 85-6. Piggyback method: the intermittent administration of a second solution through the venipuncture site of an established primary IV system.

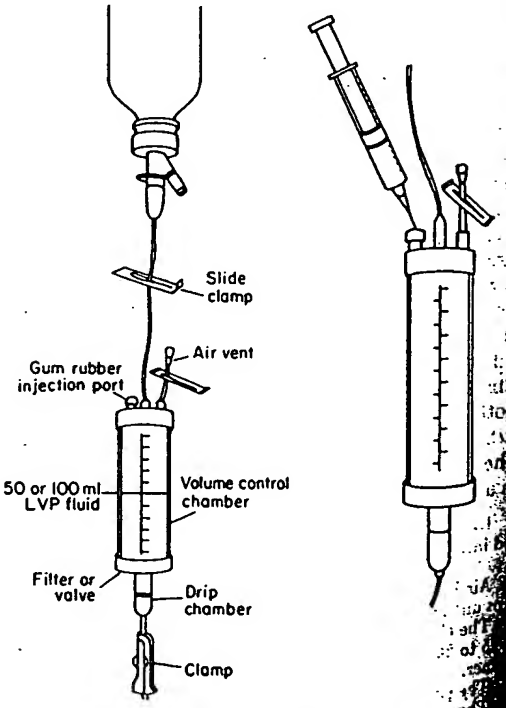

Fig. 85-7. Volume control set.

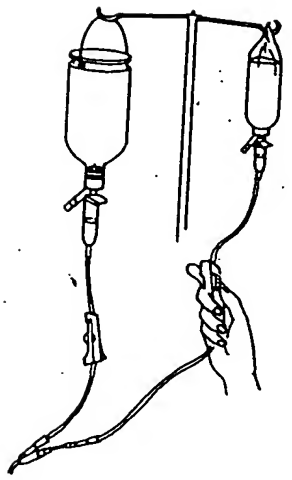

Fig. 85-8. Piggyback administration setup.

lished primary IV system. With this setup the drug can be thought of as entering the vein on "top" of the primary IV fluid, hence the designation "piggyback." The piggyback technique not only eliminates the need for another venipuncture, but also achieves drug dilution and peak blood levels within a relatively short time span, usually 30 to 60 minutes. Drug dilution helps to reduce irritation, and early high serum levels are an important consideration in serious infection requiring aggressive drug therapy. These advantages have popularized the piggyback method of IV therapy, especially for the intermittent administration of antibiotics. In using the piggyback technique, the secondary unit is purged of air and its needle inserted into a Y-injection site of the primary set or into the injection site at the end of the primary set. The piggyback infusion is then started. Once it is completed, the primary fluid infusion will be restarted. See Fig. 85-8.

Primary IV administration sets are available that have a built-in checkvalve for use in piggyback administration. When the piggyback is connected to one of these sets and started, the checkvalve automatically closes off the primary infusion. When the piggyback runs out, the check valve automatically opens, thereby restarting the primary infusion. The checkvalve works because of pressure differences. To achieve this difference, the primary container is hung lower than the secondary bottle by means of an extension hanger. See Fig. 85-9.

Several manufacturers have introduced minibottles prefilled with various antibiotic products; each container is provided with either a plastic bag or plastic hanger for direct suspension from an IV pole as the piggyback solution is administered through the resealable gum-rubber injection site of Y-type facility of an existing IV system. Reconstitution of piggyback units requires only the addition of a small volume of compatible diluent. Since reconstitution and administration proceed from the same bottle, no drug transfer is involved, so transfer syringes and additional IV containers are not necessary. Therefore prefilled piggyback units offer a greater ease in handling and a considerable reduction in inventory costs.

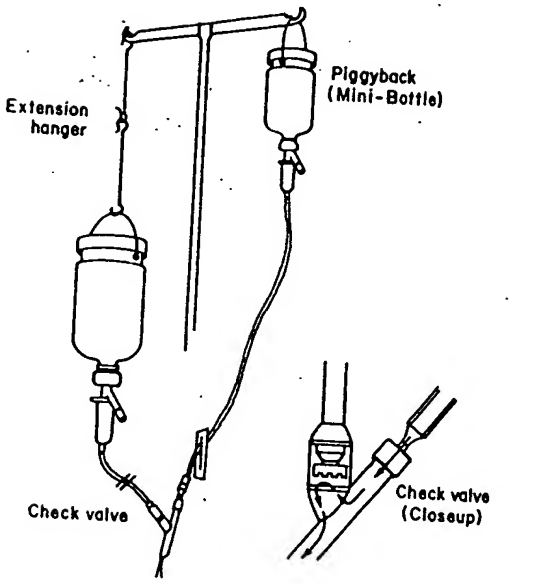

Fig. 85-9. Piggyback administration setup with check valve in primary set.

Partial-fill containers available for piggybacking are 250-ml capacity infusion bottles or bags underfilled with 50 or 100 ml Dextrose Injection, 5% or normal saline. The drug to be administered is first reconstituted in its original parenteral vial and then added by needle and syringe to the partial-fill container. The needle of the piggyback delivery system is inserted into the Y-site or gum-rubber injection port of a hanging primary infusion set. Flow of the primary intravenous fluid is stopped while the drug solution in the partial-fill container is administered (30 to 60 minutes). After the drug solution has been totally infused, the primary fluid flow is reestablished. When the next dose of drug is required, the piggyback procedure is repeated, replacing the prefilled partial-fill container.

Final Filter Devices—Particulate matter in intravenous fluids and intravenous admixtures can originate from many sources. It can result from the packaging components of the IV fluid, from admixture incompatibilities, from manipulation in preparing the admixture, and even from the administration set itself. Concern for particulate matter led to the design of final filter devices for attaching to the end of the tubing of the administration set. They afford a final filtration of the IV fluid before it passes through the needle into the vein. The device consists of a plastic chamber containing a membrane or stainless steel filter having porosities varying from 5 to 0.22 μm. Air lock can be a problem with membrane filters. When wet, membranes with a porosity of 0.22 μm and 0.45 μm are impervious to air at normal pressures and air in the system causes blockage. In order to prevent this, the filter housing must be completely purged of air prior to use. Newer device designs have air eliminators. Using final filter devices increases medication cost but reduces the biological hazards associated with particulate matter.

Intravenous Admixtures

When one or more sterile products are added to an IV fluid administration, the resulting combination is known as an intravenous admixture. To maintain the characteristics of sterile products, namely sterility, freedom from particulate matter, and pyrogens, it is imperative that they be manipulated in a suitable environment using aseptic techniques.

Environment—Proper conditions for aseptic handling can be provided by laminar airflow hoods (see Fig. 85-10 and Chapters 78, 84). Within a laminar airflow hood, air filtered through a HEPA (high efficien

Fig. 85-10. Laminar flow hoods provide the proper environment for compounding IV admixtures.

in a parallel flow configuration at a velocity of 90 ft per minute. HEPA filters remove 99.97% of all particles larger than 0.3 μm. Since microbial contaminants present in air are usually found on other particulates, removal of the latter results in a flow of air free of both microbial contaminants and particulate matter. The movement of the filtered air in a laminar flow configuration at a velocity of 90 ft per minute can maintain the area free of contamination. The flow of air may be either in a horizontal or vertical pattern. In the former case the HEPA filter is located at the back of the hood and the air flows to the front. In vertical flow the air passes through the HEPA filter located in the top of the cabinet and is exhausted through a grated area around the working surface of the hood. Regardless of the type of laminar airflow, the hood must be properly operated and maintained in order to achieve a satisfactory environment for preparing parenteral admixtures.

The hood is best situated in a clean area in which there is little traffic flow past the front of the hood. The inside of the hood is thoroughly wiped down with a suitable disinfectant and allowed to run for at least 30 minutes before starting manipulations. It is important to remember that the laminar flow hood is not a means of sterilization. It only maintains an area free of microbial contaminants and particulate matter when it has been properly prepared, properly maintained, and utilized by operators having proper aseptic techniques.

Before working in a laminar airflow hood the operator washes his hands thoroughly and scrubs them with a suitable disinfectant. Some laboratories may require gowning and use of sterile gloves. Sterile gloves can be an asset but there is always the problem that they can give the operator a false sense of security. Gloved hands can become contaminated as easily as ungloved hands. Additives and IV fluids to be used in the preparation of the admixture, along with suitable syringes, are lined up in the hood in the order they are going to be used. The containers must be clean and dust free. They are inspected for clarity and freedom from cracks. Operators are encouraged to use a lighting device for inspecting IV fluids for particulate matter and cracks. The lighting device should be of the type that permits the container to be viewed against both a light and a dark background during inspection. If the IV fluid is packaged in plastic containers, pressure is applied to assure that they are properly sealed and do not leak. Some laboratories disinfect the containers prior to placing them in the hood.

In working within the hood the operator works in the center of the hood with the space between the point of operation and the filter unobstructed. If the flow of air is blocked, then the validity of the laminar flow is destroyed. Articles are arranged within the hood in a manner to prevent clean air from washing over dirty objects and contaminating other objects that must remain sterile. The working area must be at least six inches from the front edge of the hood. As the operator stands in front of the hood, his body acts as a barrier to the laminar air flow causing it to pass around him and create backflow patterns which can carry room air into the front of the hood.

Laminar flow hoods must be maintained and evaluated periodically to insure that they are functioning properly. The velocity of air flow can be determined routinely using a velometer. Decrease in the air flow usually indicates a clogged HEPA filter. Some laminar flow hoods are equipped with pressure gauges indicating pressure in the plenum behind the filter; in these hoods pressure increase can also indicate a clogged filter. Settling plates can be exposed within the hood for given periods of time to determine the presence of microbial contaminants.

The best way to determine the proper functioning of a HEPA filter is to use the dioctyl phthalate (DOP) test. DOP is a vapor at room temperature, its vapor particles being in the range of 0.3 μm. DOP vapor is allowed to be taken up by the hood through its intake filter. If the HEPA filter is intact and properly installed, no DOP can be detected in the filtered air stream using a smoke photometer. Certification services are available through commercial laboratories; the HEPA filters within laminar flow hoods should be evaluated every six months.

Additives—The additives are injections packaged in ampuls or vials, or sterile solids; the latter are reconstituted with a suitable diluent before addition to the IV fluid. A fresh, sterile, disposable syringe is used for each additive. Before removing a measured volume from an ampul, the container is wiped with a disinfectant solution. If the ampul is scored, the top can be snapped off; if not scored, an ampul file must be used. A sterile syringe is removed from its protective wrapping. The syringe needle with its cover is separated from the syringe aseptically and may be replaced with a sterile aspirating needle. Aspirating needles are usually made from clear plastic and contain a stainless steel or nylon filter having a porosity of 5 μm. The filter will remove glass particles and other particulates from the injection as it is drawn up from the ampul into the syringe. The aspirating needle is replaced with the regular needle. The exact volume is calibrated and the injection is ready to be added to the IV fluid (see Fig. 85-11). In the case of additives packaged in multiple-dose vials, the protective cover is removed and the exposed target area of the rubber closure disinfected. A volume of air, equal to the volume of solution to be removed, is drawn up into the syringe and injected into the air space above the injection within the vial. This will facilitate withdrawal of the injection. The solution is drawn into the syringe, the exact dose is measured, and the injection is ready to be added to the IV fluid.

In the case of drug substances having poor stability in aqueous solution, the drug is packaged as a sterile solid, either dry-filled or lyophilized. The diluent recommended on the labeling is used to reconstitute the powder; the proper quantity of solution is then removed for addition to the IV fluid. When large volumes of diluent are required for reconstitution as for Keflin 4 g, a sterile needle is placed through the closure to vent the container and facilitate addition of the diluent.

The procedure for placing an additive in an IV fluid will vary depending on the type of IV fluid packaging system being used by the hospital. The packaging systems have been described in Table II.

Abbott and Cutter Rigid Glass Containers (Fig. 85-2)

1. Remove the aluminum tear seal exposing the solid rubber closure with a target circle in the center.
2. Wipe closure with suitable disinfectant.

Fig. 85-11. Placing an additive into an IV fluid with filtration through a membrane filter (courtesy, Millipore).

3. Insert needle of additive syringe through target area. The vacuum within bottle draws in the solution.
4. Gently shake the bottle after each addition.
5. When completed, cover the closure with a plastic protective cap if it is not to be used immediately.

Travenol/Baxter and McGaw Rigid Glass Containers (Fig. 85-3)

1. Remove the aluminum tear seal and the aluminum disc covering the latex diaphragm.
2. Upon exposing the latex diaphragm, note that the latex cover is drawn in over the openings in the rubber closure.
3. The larger of the two holes receives the administration set, the other is the air vent. The triangle-shaped indentation can serve as the site for injecting the additives as well as the opening for the administration set.
4. Wipe diaphragm with suitable disinfectant and pierce latex cover to place additive into bottle. The vacuum within bottle will draw additive from the syringe. Do not remove diaphragm or the vacuum will dissipate. It will be removed at the time of administration prior to the insertion of the administration set.
5. Gently shake the bottle after each additive.
6. When completed, cover the bottle with a plastic additive cap if administration set is not to be inserted immediately.

Travenol/Baxter and Abbott Plastic Container (Fig. 85-4)

1. Remove additive port protective sleeve and rub gum-rubber plug with suitable disinfectant.
2. Additives are placed in container by piercing gum-rubber cover over the additive port.
3. After each addition, milk the container to insure adequate mixing.
4. Containers do not contain a vacuum, but vacuum chambers are available for use in conjunction with the flexible plastic container.
5. Protective additive caps are available if administration set is not inserted immediately.

McGaw Semirigid Plastic Container (Fig. 85-4)

1. Remove additive port protective covering and rub gum-rubber plug with suitable disinfectant.
2. Additives are placed in containers by piercing gum-rubber over the additive port.
3. After each addition, shake the container gently to insure adequate mixing.
4. Containers do not contain a vacuum.

Parenteral Incompatibility—When one or more additives are combined with an IV fluid, their presence together may modify the inherent characteristics of the drug substances present, resulting in a parenteral incompatibility. Parenteral incompatibilities have been arbitrarily divided into three groups: physical, chemical, and therapeutic. The last are the most difficult to observe because the combination results in undesirable antagonistic or synergistic pharmacological activity. For example, the report that penicillin or cortisone antagonizes the effect of heparin and produces a misleading picture of the anticoagulant effect of heparin represents a therapeutic incompatibility. Physical incompatibilities are the most easily observed and can be detected by changes in the appearance of the admixture, such as a change in color, formation of a precipitate, or evolution of a gas. Physical incompatibilities frequently can be predicted by knowing the chemical characteristics of the drugs involved. For example, the sodium salts of weak acids, such as phenytoin sodium or phenobarbital sodium, precipitate as free acids when added to intravenous fluids having an acidic pH. Calcium salts precipitate when added to an alkaline medium. Injections that require a special diluent for solubilization, such as Valium, precipitate when added to aqueous solutions because of their low water-solubility.

Decomposition of drug substances resulting from combination of parenteral dosage forms is called a chemical incompatibility, an arbitrary classification since physical incompatibilities also result from chemical changes. Most chemical incompatibilities result from hydrolysis, oxidation, reduction, or complexation and can be detected only with a suitable analytical method.

An important factor in causing a parenteral incompatibility is a change in the acid-base environment.[1] The solubility and stability of a drug may vary as the pH of the solution changes. A change in the pH of the solution may be an indication in predicting an incompatibility, especially one involving drug stability, since this is not necessarily apparent physically. The effect of pH on stability is illustrated in the case of penicillin. The antibiotic remains active for 24 hr at pH 6.5, but at pH 3.5 it is destroyed in a short time. Potassium penicillin G contains a citrate buffer and is buffered at pH 6.0 to 6.5 when reconstituted with Sterile Water for Injection, Dextrose Injection, or Sodium Chloride Injection. When this reconstituted solution is added to an intravenous fluid such as Dextrose Injection or Sodium Chloride Injection, the normal acid pH of the solution is buffered at pH 6.0 to 6.5, thus assuring the activity of the antibiotic.

While it may be impossible to predict and prevent all parenteral incompatibilities, their occurrence can be minimized. The IV admixture pharmacist should be cognizant of the increasing body of literature concerning parenteral incompatibilities. This includes compatibility guides published by large-volume parenteral manufacturers;[2,3,4] compatibility studies on individual parenteral products by the manufacturer and published with the product as part of the labeling; the study of the National Coordinating Committee on Large-Volume Parenterals;[5] reference books;[6,7] and literature reports of studies with specific parenteral drugs.[8] The pharmacist should encourage use of as few additives as possible in intravenous fluids since the number of potential problems increases as the number of additives increases. Physicians should be made aware of possible incompatibilities and the pharmacist can suggest alternate approaches to avoid the difficulties. In some instances, incompatibilities can be avoided by selecting another route of administration for one or more of the drugs involved.

Quality Control—Each hospital should have written procedures covering the handling and storage of IV fluids, their use in preparing admixtures, labeling, and transportation to the floors. In-use clarity and sterility tests should be devised to assure that IV admixtures retain the characteristics of sterility and freedom from particulate matter. Training and monitoring personnel involved in preparation of IV admixtures should be done on a regular basis.[9] The efforts of the hospital pharmacy should be no less than those of the industry in following Current Good Manufacturing Practice to assure the safety and efficacy of these compounded medications.

Total Parenteral Nutrition

Intravenous administration of calories, nitrogen, and other nutritients in sufficient quantities to achieve tissue synthesis and anabolism is called total parenteral nutrition (TPN).[10] Originally the term hyperalimentation was used to describe the procedure, but it is being replaced by TPN, the latter being more descriptive for the technique.

The normal calorie requirement for an adult is approximately 2500 per day. If these were to be provided totally by Dextrose Injection 5%, approximately 15 liters would be required. Each liter contains 50 g dextrose, equivalent to 170 calories. However, it is only possible to administer three or four liters per day without causing fluid overload. To reduce this fluid volume the concentration of dextrose would have to be increased. By increasing the dextrose to 25%, it is possible to administer five times the calories in one-fifth the volume. Dextrose Injection 25% is hypertonic and cannot be administered in large amounts into a peripheral vein without sclerosing the vein.

Dudrick developed the technique for administering fluids for total parenteral nutrition by way of the subclavian vein into the superior vena cava where the solution is rapidly diluted by the large volume of blood available, thus minimizing the hypertonicity of the solution. For administration of the TPN fluids, a catheter is inserted and retained in place in the subclavian vein. TPN is indicated in patients who are unable to ingest food due to carcinoma or extensive burns; patients who refuse to eat, as in the case of depressed geriatrics or young patients suffering from anorexia nervosa; and surgical patients who should not be fed orally.

The preferred source for calories in TPN fluids is the carbohydrate dextrose. Both fat emulsions and alcohol are caloric sources, but they are not used in TPN fluids. In IV fluid kits commercially available for the preparation of TPN solutions, Dextrose Injection 50% is provided. On dilution with protein hydrolysate or amino acid injection, the resulting dextrose concentration is approximately 25%. It is this concentration that is administered.

The source of nitrogen in TPN fluids is either protein hydrolysates (*Amigen*®—Travenol; *Aminosol*®—Abbott; *CPH-5*®—Cutter; *Hyprotigen*®—McGaw) or crystalline amino acids (*Aminosyn*®—Abbott; *FreAmine II*®—McGaw; *Travasol*®—Travenol; *Veinamine*®—Cutter). Protein hydrolysates are obtained from casein or fibrin and contain polypeptides which must be broken down before they can be utilized. Although available at lower cost than crystalline amino acids, they contain higher amounts of ammonia and free chloride. In the case of hydrolysates, the exact amount of protein being administered is not known. The crystalline amino acid injections contain all the essential and nonessential amino acids in the L-form. They are more expensive than the protein hydrolysates but contain less ammonia and free chloride. For optimum utilization of amino acids and for promoting tissue regeneration, the nitrogen-to-calorie ratio should be 1:150. Calories are needed to provide energy for the metabolism of nitrogen.

Electrolyte requirements will vary with the individual patient. The electrolytes present in Protein Hydrolysate Injection or Amino Acid Injection are given on the label and must be taken into consideration in determining the quantities to be added. Usual electrolyte concentrations required to fall within the following ranges: sodium, 100–120 mEq; potassium, 80–120 mEq; magnesium, 8–16 mEq; calcium, 5–10 mEq; chloride, 100–120 mEq; and phosphate, 40–60 mEq. It is better to keep a 1:1 ratio between sodium and chloride ions. In adding potassium, the acetate salt is preferred to the chloride. If the combination of calcium and phosphate ions exceeds 20 mEq, precipitation occurs.

In addition to the electrolytes, the daily requirement for both water-soluble and fat-soluble vitamins may be added, usually in the form of a multivitamin infusion concentrate. Iron, folic acid, and vitamin B_{12} should be administered separately from the TPN fluids. Trace elements such as zinc, copper, manganese, and iodide are a concern only in long-term cases and can be added when required.

The Parenteral Prescription

The physician writes an admixture order or parenteral prescription on a physician's order-form located on the patient's chart. A copy of the order is sent to the pharmacy for compounding. It includes the patient's name, room number, the intravenous fluid wanted, additives and their concentrations, rate of flow, starting time, and length of therapy. The order is taken by the technician, nurse, or pharmacist to the pharmacy. Orders may be telephoned to the pharmacy; verification with the original order is made on delivery of the admixture. IV orders are usually written for a 24-hour therapy period; the patient's chart is reviewed daily and new orders are written on a daily basis. The order may be for multiple containers, in which case the containers are numbered consecutively. Unlike the extemporaneously compounded prescription, additives are added without regard to final volume of IV fluid. The prescription is checked for proper dose, compatibility, drug allergies, and stability. Additives are usually given an expiration period of 24 hours from time of preparation. Drugs such as ampicillin may require shorter expiration periods.

The clerical work for the admixture is prepared. This includes typing of the label and the preparation of the profile work sheet. The profile sheet is filed so that the pharmacist will be alerted when subsequent containers are due for preparation. Charging the patient's account can be done from the profile work sheet. The label includes the patient's name, room number, bottle number, preparation date, expiration time and date, intravenous fluid and quantity, additives and quantities, total time for infusion, the milliliters per hour, drops per minute, and space for the name of the nurse who hangs the container. The label will be affixed to the container upside down in order that it can be read when hung.

The admixture is prepared by the pharmacist or a supervised technician. In handling sterile products, aseptic techniques as discussed previously must be observed. When completed, a plastic additive cap is affixed before delivery to the floor. The label is applied and checked with the original order. The empty additive containers are checked to verify the additives present. The admixture is inspected for color change or particulate matter.

Table III—Typical IV Orders (Parenteral Prescriptions)

Prescription	Comment
1. ℞ NSS 1000 ml 125 ml/hr	Sodium Chloride Injection (Normal Saline Solution) 1000 ml, is to be administered at the flow-rate of 125 ml per hour. It will require approximately eight hours.
2. ℞ 1000 D5 NSS + Vits 12 hr	Dextrose Injection 5%, 1000 ml, containing 0.9% sodium chloride and container of vitamin B complex with vitamin C is to be administered over a 12-hour period.
3. ℞ 500 D5 ½NSS KVO	Dextrose Injection 5%, 500 ml, containing 0.45% sodium chloride is to be administered at a rate of flow to keep the vein open (KVO). The flow rate will be approximately 10 ml per hour.
4. ℞ 1000 cc D5/½NSS Add 1 amp Vits to each + 100 mg Thiamine Each to run 6 hr	Dextrose Injection 5%, 1000 ml, containing 0.45% sodium chloride, the contents of one ampul vitamin B complex with vitamin C, and sufficient volume of Thiamine Hydrochloride Injection to give 100 mg thiamine, is to be administered over a 6-hour period (approximately 170 ml per hour). Additional orders of the same can be anticipated.
5. ℞ 1000 cc D5/½ NSS + 20 mEq KCl	Dextrose Injection 5%, 1000 ml, is to be provided containing 0.45% sodium chloride and 20 mEq potassium chloride.
6. ℞ 1000 Hyperal + 10 NaCl + 10 KCl + 5 $MgSO_4$ + 10 Insulin	One liter of the hospital's basic TPN solution is to be provided with the addition of 10 mEq sodium chloride, 10 mEq potassium chloride, 5 mEq magnesium sulfate, and 10 units regular zinc insulin.
7. ℞ 1000 cc Hyperal (FreAmine) + 40 mEq $NaHCO_3$ + 30 mEq KCl + Vits + 5u Reg Insulin to run 80 cc/hr	One liter of the basic TPN solution, FreAmine II, is to be provided with the addition of 40 mEq $NaHCO_3$, 30 mEq potassium chloride, the contents of one container vitamin B complex with vitamin C plus 5 units of regular zinc insulin. It is to be administered at the flow rate of 80 ml per hour (approximately 12 hours).
8. ℞ 1000 Hyperal + 40 mEq NaCl + 10 KCl + 10 Insulin + 10 Cal Gluc.	One liter of the hospital's basic TPN solution is to be provided with the addition of 40 mEq sodium chloride, 10 mEq potassium chloride, 10 units regular zinc insulin, and 10 ml Calcium Gluconate Injection.
9. ℞ Keflin 2 gm 100 ml D_5W q 6 hr	Cephalothin, 2 g, is reconstituted with Sterile Water for Injection and added to a minibottle containing 100 ml Dextrose Injection 5%. This dose is given every 6 hours using a piggyback technique with a flow rate requiring 30 to 60 minutes for delivery.
10. ℞ Gentamicin 80 mg IVPB q 8 hr	Gentamicin, 80 mg, is added to a minibottle containing 100 ml Dextrose Injection 5%. This dose is given every 8 hours using the piggyback technique (IVPB) with a flow-rate requiring at least 80 minutes (not less than 1 mg per minute).

The completed admixture is delivered to the floor. If it is not to be infused immediately (within one hour), it is stored under refrigeration; if refrigerated, it must be used within 24 hours. The nurse checks for accuracy of patient's name, drug and concentration, IV fluid, expiration date, time started, and clarity. The infusion of admixtures can run ahead or behind schedule, necessitating the pharmacist to modify the preparation of continued orders. Examples of IV orders are shown in Table III.

References

1. Newton DW: Physicochemical determinants of incompatibility and instability of injectable drug solutions and admixtures. *Am J Hosp Pharm 35*: 1213, 1978.
2. King JC: Guide to Parenteral Admixtures. Cutter Laboratories, Berkeley, CA, 1973.
3. Shoup LK, Goodwin NH: Implementation Guide—Centralized Admixture Program. Travenol Laboratories, Morton Grove, IL, 1977.
4. Good IV Procedures Manual. Abbott Laboratories, North Chicago, IL, 1979.
5. Bergman HD: Incompatibilities in large-volume parenterals. *Drug Intell Clin Pharm 11*: 345, 1977.
6. Trissel LA: *Parenteral Drug Information Guide.* Am Soc Hosp Pharm, Washington, DC, 1974.
7. Trissel LA: *Handbook on Injectable Drugs.* Am Soc Hosp Pharm, Washington, DC, 1977.
8. Kobayashi NH, King JC: Compatibility of common additives in protein hydrolysate/dextrose solutions. *Am J Hosp Pharm 34*: 589, 1977.
9. Sanders SJ, Mabadeje SA, Avis KE, Cruze CA, Martinez DR: Evaluation of compounding accuracy and aseptic techniques for intravenous admixtures. *Am J Hosp Pharm 35*: 531, 1978.
10. Dudrick SJ, Rhoads JE: Total intravenous feeding. *Sci Amer 226*: 73, 1972.

Bibliography

Turco SJ, King RE: *Sterile Dosage Forms: Their Preparation and Clinical Applications*, 2nd ed, Lea & Febiger, Philadelphia, 1979.

Trissel LA: *Handbook on Injectable Drugs*, Am Soc Hosp Pharm, Washington, DC, 1977.

National Coordinating Committee on Large-Volume Parenterals: Recommended methods for compounding intravenous admixtures in hospitals. *Am J Hosp Pharm 32*: 261, 1975.

Francke DE, ed: *Handbook of IV Additive Reviews*, Drug Intelligence Publications, Hamilton, IL, 1970, 1971, 1972, 1973.

IV Additives and Sterile Technology, Am Soc Hosp Pharm, Washington, DC, 1975.